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A RANDOMIZED CONTROLLED TRIAL OF TWO KETOGENIC DIETS IN THE TREATMENT OF CHILDHOOD EPILEPSY

Thesis submitted for the Degree of Doctor of Philosophy

by

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DECLARATION

I, Elizabeth Grace Neal, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Elizabeth Grace Neal

ABSTRACT

This thesis describes the first randomized controlled trial on the ketogenic diet as a treatment for children with drug-resistant epilepsy. It asks two main questions. Firstly, are there clear benefits on seizure control in children treated with the ketogenic diet as compared with no additional treatment?; and secondly, is the classical ketogenic diet more efficacious than the medium chain triglyceride (MCT) ketogenic diet, as often claimed but not supported by scientific evidence? The trial also examines the tolerability of the two diets, and their effect on growth.

145 children were randomized to receive the classical or MCT diet, either immediately or after a 3-month delay with no change in treatment (control group). Seizure frequency was assessed after 3 months, compared to that of controls. Efficacy and tolerability of the two diets was compared at 3, 6 and 12 months. Growth was assessed during the study period. Clear guidelines on calculation of both diets were developed, as was an electronic ketogenic calculator to reduce the burden of time spent on recipe calculations.

Results show children on a ketogenic diet to have significantly reduced numbers of seizures after 3 months, as compared to the control group. Despite increased ketone levels in classical diet children, there was no difference in efficacy between the two diets at 3, 6 or 12 months. There was no difference in gastro-intestinal tolerability; both diets caused increased cholesterol levels, but increased triglyceride levels were seen in the classical group only. Many children did show compromised growth during the study, but after 12 months, there was no significant difference in growth outcome between the two diets.

These results strongly support using the ketogenic diet in childhood epilepsy. Classical and MCT diets are comparable in efficacy, tolerability and growth outcomes; both protocols continue to have their place in the treatment of this group of children.

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CHAPTER 1

THE KETOGENIC DIET IN CHILDHOOD EPILEPSY

Contents

1.1 Epilepsy - background, definitions and epidemiology

Epilepsy is the most prevalent of the serious neurological disorders. The name derives from the Greek verb 'to be seized'. Historically, by definition the diagnosis has required at least two epileptic seizures. The most recent proposal by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) defines epilepsy as a 'disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition' (Fisher et al, 2005); at least one epileptic seizure is required for this definition. Seizure activity is caused by an abnormal and excessive discharge from the neurons in the brain, and manifests as alterations in sensation, behaviour, or consciousness, and in some cases, as purely electrical activity, discernable only on electroencephalography (EEG).

Seizure types can broadly be divided into two groups – those arising from a single location, or focus, within the brain, termed focal seizures, and those of a more generalized nature. ILAE proposals for a new diagnostic scheme for people with epilepsy (Engel, 2001) include updated guidelines for seizure classification (see Table 1.1).

Table 1.1 ILAE classification of epileptic seizure types (from Engel, 2001)

Many types of epilepsy can be classified into syndromes, based on clinical features, EEG results, associated development and learning, and a range of other factors such as family history, age of onset, and response to treatment. The classification proposed by the ILAE in 1989 further divided epilepsies into idiopathic,

symptomatic, or cryptogenic, depending on the suggested cause of the disease (Anonymous, 1989). 'Idiopathic' generally refers to genetic syndromes with no associated brain pathology; 'symptomatic' epilepsies are the result of a known brain disorder, and 'cryptogenic' epilepsies are the result of a brain disorder that cannot be identified. Despite updated ILAE proposals for syndrome classification removing these labels (Engel, 2001), they are still widely used in clinical practice.

The overall incidence of epilepsy ranges between 40 to 70 per 100,000 per year in developed countries and 100 to 190 per 100,000 in developing countries (Guberman & Bruni, 1999). It is highest in early childhood and old age, with 50 – 60% of epilepsy beginning before the age of 16 years. The prevalence of epilepsy is between 5 and 10 cases per 1000 persons (Bell & Sander, 2001); rates being influenced by the definition used for 'active' epilepsy (generally taken as one or more seizures in the previous five years).

1.2 Prognosis and treatment

A range of anti-epileptic medication is available for use in the treatment of seizures; this is usually commenced after presentation of two or more unprovoked seizures. Literature reports on prognosis suggest approximately 70% of patients can achieve long-term remission from seizures (Annegers et al, 1979; Goodridge & Shorven, 1983; Cockerell et al, 1997; Sanders, 1993). In a study examining progress of 417 children with epilepsy over 8 years, Camfield et al (1997) reported that 61% of children who were taking one anti-epileptic medication in the first year of treatment were seizure free at the end of the study period. 17% of children needed to have an additional medication; 42% of this group subsequently became seizure-free.

Medication is usually the first line of choice in epilepsy treatment. However, there is a minority of individuals for whom this is unsuccessful, with continued seizure activity; this group is termed drug-resistant or intractable. This definition of intractability frequently refers to failure of at least two appropriate anti-epileptic medications, but has been much debated, particularly in the context of criteria for on-going referral and treatment (Berg & Kelly, 2006). Intractability is of particular concern in children, where on-going seizure activity may impact on development. Although the seizure type can help in predicting prognosis, with focal seizures less likely to remit than generalized (Bell & Saunder, 2001), the specific epilepsy syndrome will be more predictive, and likely to indicate any associated neurological and mental morbidity (Shinnar, 1994) (see Table 1.2).

Table 1.2 Prognosis for seizure remission and/or neurological deterioration, based on syndrome type (from Guberman & Bruni, 1999)

Treatment options for patients with intractable epilepsy are more limited, and include surgery (suitable in only a minority of candidates), vagal nerve stimulation, and the ketogenic diet.

1.3 Development of the ketogenic diet

Earliest reports of the effect of starvation on epilepsy date back to the 5th century, when Hippocrates described a man whose seizures were cured by abstaining from all food and drink. Other renowned early physicians who advocated the role of diet in epilepsy were Galen and Avicenna. First reports in the medical literature were by Guelpa and Marie (1911), who described the cessation of seizures during complete fasting. This idea was not taken up until 1921, when Geyelin also reported the successful use of fasting to treat epilepsy. He found that 20 out of 26 fasted patients had improved seizure control, two of who remained seizure free for more than a year. The arbitrary length of fasting was 20 days, however only four had seizures after the tenth day without food. Geyelin was inspired by the work of an osteopath named Conklin (1922) who believed that epilepsy was caused by intoxication from the Peyer's patches of the intestine and therefore advocated complete gut rest. Conklin fasted his patients for up to 25 days, and reported a 90% success rate in children under the age of 10 years, decreasing to 50% in adults. These observations sparked considerable clinical and research interest, and linked in with ongoing studies examining ketoacidosis and the disturbance in glucose metabolism that occurs in diabetes.

During fasting, the body passes through various phases of hormonal and metabolic adaptation in an attempt to spare protein breakdown and to draw on the energy reserves of body fat. The muscles and other tissues progressively switch their

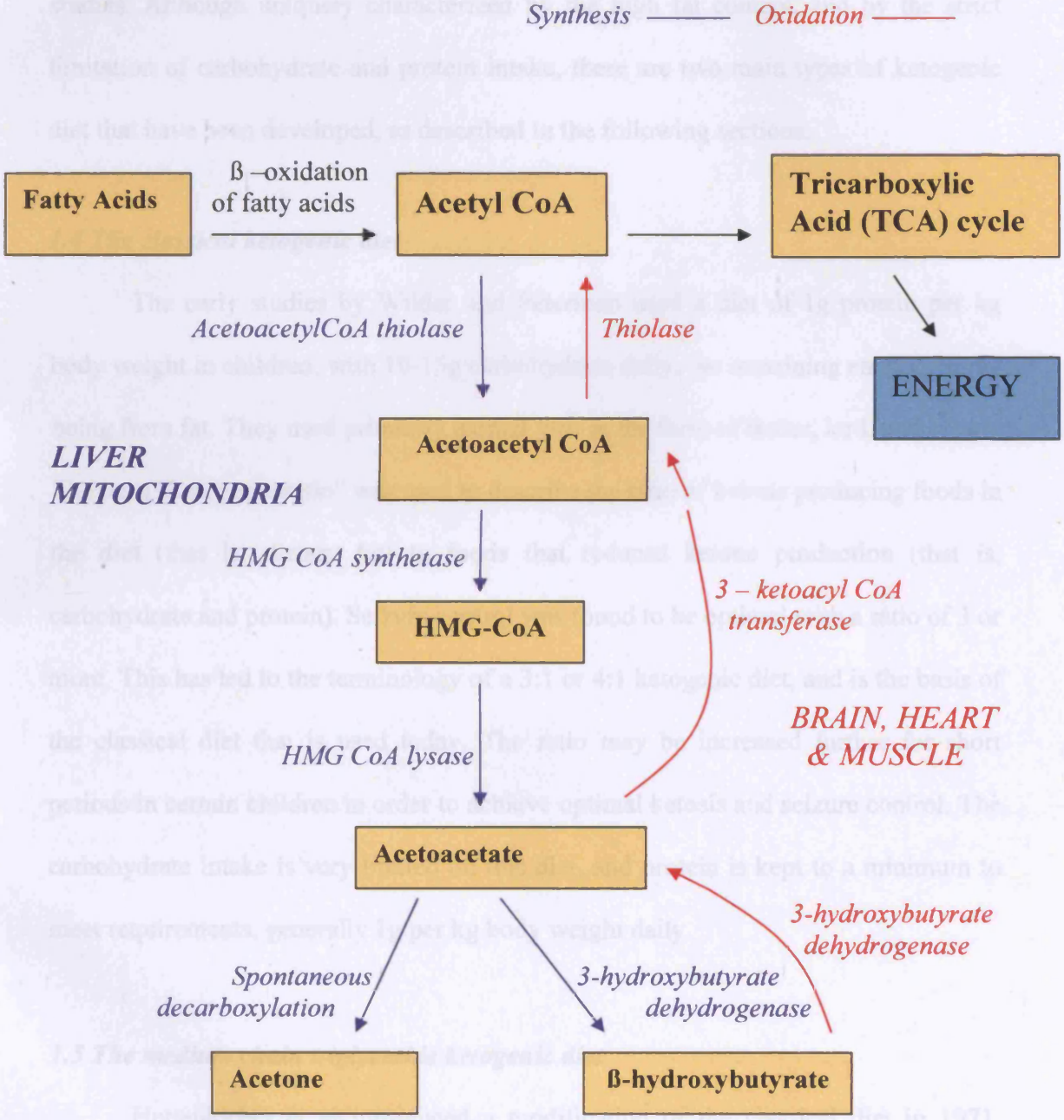
energy source from glucose to free fatty acids. ß-oxidation of these fatty acids results in the formation of acetyl-CoA, and this can be converted into ketone bodies (acetoacetate and β-hydroxybutyrate), by a five-step pathway that takes place in liver mitochondria (see Figure 1.1). Ketone bodies, in contrast to fatty acids, are able to pass across the blood-brain barrier, and as their levels rise in the blood, will be increasingly utilized for energy by the brain, heart and muscle. They are converted back to acetyl CoA, which enters the tricarboxylic acid cycle. Blood levels of ketones will continue to increase during the first two weeks of starvation, until the brain becomes dependent on them for energy. Serum bicarbonate is also reduced, with a compensated metabolic acidosis.

Use of fasting to treat epilepsy had obvious clinical limitations, and it was therefore suggested by Wilder (1921) that a diet high in fat and low in carbohydrate might mimic the ketotic effect. A restriction of dietary carbohydrate would limit glucose supply, and as fat is metabolized to ketone bodies, these would be used as the alternative fuel. Wilder went on to find that 50% of his patients at the Mayo Clinic had significant seizure control on this "ketogenic" diet. Peterman (1925), a fellow worker at the clinic, reported further successful results in a group of 37 patients, with 95% showing improvement when treated by the diet.

In 1927, Talbot and his co-workers were able to show that this ketogenic diet did cause similar biochemical changes to fasting. They introduced the idea of an initial fast before commencing the diet, with a gradual build up of dietary fat over the following few days. The diet was subsequently shown to have a use in seizure control by many other workers (Helmholtz (1927), Lennox (1928), Mc Quarrie & Keith (1929), Wilkins (1937)). It was widely used throughout the 1930s, and was found to be most successful in children, who produce and use ketones more rapidly, and have

fewer problems with compliance. Although there are a few reports in the literature of successful use of the diet in adults (Sirven et al, 1999), it is primarily used in childhood epilepsy.

Figure 1.1 Summary metabolic pathways of ketone body synthesis and oxidation



The development of new anticonvulsant medication at the end of the 1930's detracted interest away from the ketogenic diet, but a realization that not all children do respond to medications, and concerns about their side effects, has maintained interest in alternative treatments, and there has been renewed research interest in the diet over the past ten years. The basic dietary principles remain the same as in early studies. Although uniquely characterized by the high fat content, and by the strict limitation of carbohydrate and protein intake, there are two main types of ketogenic diet that have been developed, as described in the following sections.

1.4 The classical ketogenic diet

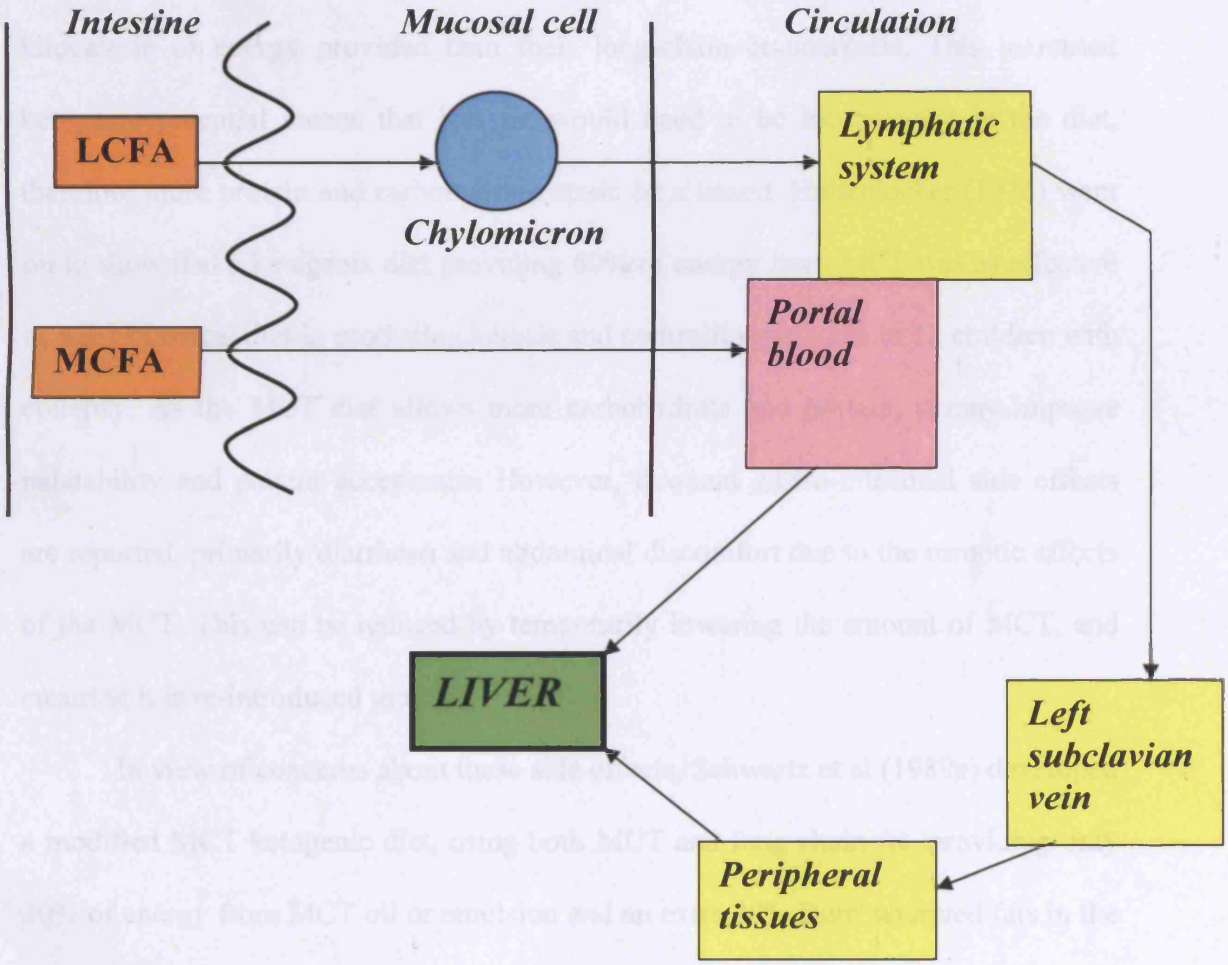
The early studies by Wilder and Peterman used a diet of 1g protein per kg body weight in children, with 10-15g carbohydrate daily, the remaining energy supply being from fat. They used primarily animal fats, in the form of butter, lard, and cream. The term "ketogenic ratio" was used to describe the ratio of ketone producing foods in the diet (that is, dietary fat) to foods that reduced ketone production (that is, carbohydrate and protein). Seizure control was found to be optimal with a ratio of 3 or more. This has led to the terminology of a 3:1 or 4:1 ketogenic diet, and is the basis of the classical diet that is used today. The ratio may be increased further for short periods in certain children in order to achieve optimal ketosis and seizure control. The carbohydrate intake is very limited on this diet, and protein is kept to a minimum to meet requirements, generally 1g per kg body weight daily.

1.5 The medium chain triglyceride ketogenic diet

Huttenlocher et al introduced a modification of the classical diet in 1971, using medium chain triglycerides (MCT) as an alternative fat source. The main constituents of MCT are the medium chain length octanoic and decanoic fatty acids,

which are absorbed more efficiently than their long chain counterparts, and carried directly to the liver in the portal blood. This is in contrast to long chain fatty acids, which are incorporated into chylomicrons and transported via the thoracic duct through the lymph system to the left subclavian vein, where they exit into the circulation, and are carried via the peripheral tissues to the liver (Figure 1.2).

Figure 1.2. Differential medium and long chain fatty acid metabolism



LCFA = long chain fatty acids
MCFA = medium chain fatty acids

Following hepatic tissue uptake, there are further differences between long and medium chain fat metabolism. Long chain fatty acids will be firstly bound to carnitine; this is necessary for their transport across the mitochondrial membrane, into the liver mitochondria where ß-oxidation and ketone body synthesis occurs. This carnitine shuttle system is not necessary for medium chain fatty acids, which will enter mitochondria directly.

These differences in MCT metabolism will facilitate more rapid and greater oxidation of medium chain fatty acids, resulting in a higher ketone yield per kilocalorie of energy provided than their long-chain counterparts. This increased ketogenic potential means that less fat would need to be incorporated in the diet, therefore more protein and carbohydrate could be allowed. Huttenlocher (1976) went on to show that a ketogenic diet providing 60% of energy from MCT was as effective as a 3:1 classical diet in producing ketosis and controlling seizures in 12 children with epilepsy. As the MCT diet allows more carbohydrate and protein, it may improve palatability and patient acceptance. However, frequent gastro-intestinal side effects are reported, primarily diarrhoea and abdominal discomfort due to the osmotic effects of the MCT. This can be reduced by temporarily lowering the amount of MCT, and ensuring it is re-introduced gradually.

In view of concerns about these side effects, Schwartz et al (1989a) developed a modified MCT ketogenic diet, using both MCT and long chain fat, providing only 30% of energy from MCT oil or emulsion and an extra 30% from saturated fats in the form of butter or cream; this became known as the John Radcliffe diet.

1.6 Availability and efficacy of the ketogenic diet

Worldwide use of the ketogenic diet has increased dramatically since the early 1990s. Although the largest numbers of centres offering this treatment are in the United States, a recent survey reported ketogenic diet programs in 41 other countries, 16 of which had multiple centres (Kossoff & McGrogan, 2005). Most geographic regions were represented, with the exception of the majority of Africa and Central America. Although most of the larger centres in the United States currently use a classical protocol, European and worldwide ketogenic diet practice is more varied, with both classical and MCT diets being employed; the choice often being influenced with how easily such a diet fits in with local food choices. Both protocols are currently used within the UK; a postal survey of 250 British Dietetic Association Paediatric Group members was conducted in 2000 (Magrath et al, 2000). Of the 127 replies, 22 centres were using the ketogenic diet. 13 used the classical protocol (59%), and 9 the MCT protocol (41%).

Despite increasing worldwide usage of the ketogenic diet, and extensive recent media and internet coverage on the subject, many hospitals, even those specializing in paediatric neurology, are unable to provide the treatment for their paediatric patients with epilepsy. Nearly all centres in Europe report being limited by a lack of dietetic time and resources (Kossoff & McGrogan, 2005). Neurologists are becoming more aware of the diet, but most continue to reserve its use until a child has failed a number of anticonvulsants; the main reasons for this reluctance being lack of dietetic resources, and uncertainty about efficacy (Hemingway et al, 2001b).

So does the ketogenic diet work? Many studies have reported excellent success rates in treating seizures in children with intractable epilepsy, and most health professionals working in this field can provide numerous anecdotal reports of success.

It has also been used as a successful early therapy before epilepsy becomes intractable (Rubenstein et al, 2005). Lefevre & Aronson systematically reviewed 11 studies in 2000 and concluded there was sufficient evidence to determine that the diet is efficacious in children with intractable epilepsy, although they were concerned about the lack of controlled trials. All 11 studies were observational, only 2 were prospective, one being a United States multi-centre trial. An updated review of 14 studies (Keene, 2006) made the same conclusion, but also found no prospective controlled studies. This problem was highlighted in a Cochrane review, which failed to find any randomized controlled trials on the ketogenic diet (Levy & Cooper, 2003), despite ILAE recommendations that such trials should be included among the required criteria for assessing efficacy and tolerability of an antiepileptic agent (Anonymous, 1989). A randomized controlled trial is clearly necessary to validate the reported benefits of using the ketogenic diet in children with epilepsy. Positive results in such a trial would enable increased resources to be channeled into this area of work, and thus improve availability of the diet for those children who need it.

1.7 Comparison between the classical and MCT ketogenic diets

There have been many recent claims that the classical ketogenic diet is more efficacious in treating seizures than the MCT diet, mainly originating from centres in the United States. These cannot be backed by scientific evidence, as studies comparing the efficacy of the two types of diet are very limited. Livingstone et al (1977) examined results on 600 patients following the classical 3:1 ketogenic diet and 25 following the MCT diet, and concluded that only those on the classical diet responded. This was an uncontrolled study, with the difference in sample size of each group being too large for statistical analysis. Berman (1978) also compared the two

diets in a small, uncontrolled group of children, using the 4:1 ratio for the classical diet, and concluded that the MCT diet was less effective.

Schwartz et al (1989a, 1989b) compared the clinical and metabolic effects of three types of ketogenic diet – the classical 4:1 diet, the traditional MCT oil diet (60% energy as MCT), and the modified MCT diet (30% energy as MCT). 55 children and 4 adults were studied. 15 patients received the classical diet alone, 22 received the MCT diet alone (including the four adults), 13 received the modified diet alone, and nine were given the MCT diet for at least 33 months, then changed to the classical diet. They found all three diets equally effective in controlling seizures in children under the age of 15 years. However the diets were chosen as deemed the most appropriate for the child and family in this study, and not randomized; therefore results could be influenced by substantial selection bias.

The classical diet can seem unpalatable due to such a high fat and low carbohydrate content. Fat sources would be butter, mayonnaise, margarine, oil, cream or a prescribable long chain fat supplement. Starchy foods such as cereals, bread, potato or rice are generally not allowed, the main carbohydrate sources being a limited portion of vegetables or fruit. Meat, fish, egg or cheese would provide protein at each meal, but it is difficult to include protein foods that contain additional sources of carbohydrate, such as sausages, fish fingers or milk. The MCT diet allows considerably more carbohydrate and protein, thus the incorporation of a wider range of food choices. This has led many to argue that it is easier to comply with, but the risk of gastro-intestinal side effects must be considered. Schwartz et al (1989a) found no problems with the fat content of the classical diet, however large amounts of MCT oil were unpalatable. For this reason, many centres using the MCT diet will use a

modified protocol, although at this reduced level of MCT, there may be problems obtaining adequate levels of ketosis.

1.8 Aim of this study

In view of the lack of randomized trials comparing the classical and MCT ketogenic diets, and the lack of any controlled trials on either diet as a treatment for childhood epilepsy, a randomized controlled trial on these two dietary protocols was designed. The aim of this study was to conduct such a trial, and in particular to address the following questions.

Are there clear benefits in terms of seizure control in the group of children with epilepsy treated with a ketogenic diet as compared to a control group?

This will be examined by the randomization of children to an immediate or delayed start to one of the two diets, providing a group who act as their own controls, against which the efficacy of the diets could be compared. Records of seizure activity using a specially designed chart, EEG recordings, and documentation of changes in anti-epileptic medications will be used to assess efficacy. Chapter 3 evaluates the literature on efficacy of the ketogenic diet, and reports results of this trial.

Is the classical ketogenic diet more efficacious than the MCT ketogenic diet in controlling seizures, as often claimed but not supported by scientific evidence?

This will be examined by randomization of children to either a classical or MCT protocol for the ketogenic diet. The methods described above will be used to assess efficacy. This subject is also discussed in chapter 3, where results are reported.

How do the classical and MCT ketogenic diets compare in terms of tolerability?

Although it is often assumed that the increased carbohydrate provided by the MCT diet allows better tolerability and easier use, the gastro-intestinal side effects of MCT may cause problems. This question will be examined by comparing the tolerability of the classical and MCT diets, using a parental questionnaire. Reasons for any early failures will be examined and other side effects that may occur on the diet also reported. Chapter 4 explores the literature on this subject, and reports results.

Does the restricted ketogenic diet affect growth of children with epilepsy, and are there any differences between the classical or MCT diets?

In view of the risk of growth problems in children following a restricted diet, weight and height changes of children on both classical and MCT ketogenic diets will be closely monitored. Results are reported and discussed in chapter 5.

What conclusions can be drawn from this study and where do we go from here?

Chapter 6 concludes the thesis and looks at where we may go from here. Although the primary aim of the study was to conduct the randomized controlled trial as described, the results will also provide further information that will be important in the eventual development of national best practice guidelines for use of the ketogenic diet.

CHAPTER 2

METHODOLOGY, DIETETICS AND THE DEVELOPMENT OF RESOURCES

Contents

2.1 Subjects and inclusion criteria

Subjects were children from the UK with a diagnosis of epilepsy who had been referred by their local consultant paediatrician to one of the two consultant paediatric neurologists heading the study. The majority of children were seen at Great Ormond Street Hospital, London, although a few children were recruited additionally from Central Middlesex Hospital, London, and the National Centre for Young People with Epilepsy, Lingfield (residential centre). Subjects had to fulfill the following inclusion criteria:

- Aged between 2 and 16 years
- At least 7 seizures weekly
- Tried at least 2 anti-epileptic medications

- No previous treatment with the ketogenic diet
- Families or other carers understand the implications of the diet and are contactable for regular monitoring while at home
- No history of hyperlipidaemia or renal stones
- No enzyme deficiencies of organic acid metabolism (all children screened by urine test).

2.2 Study design

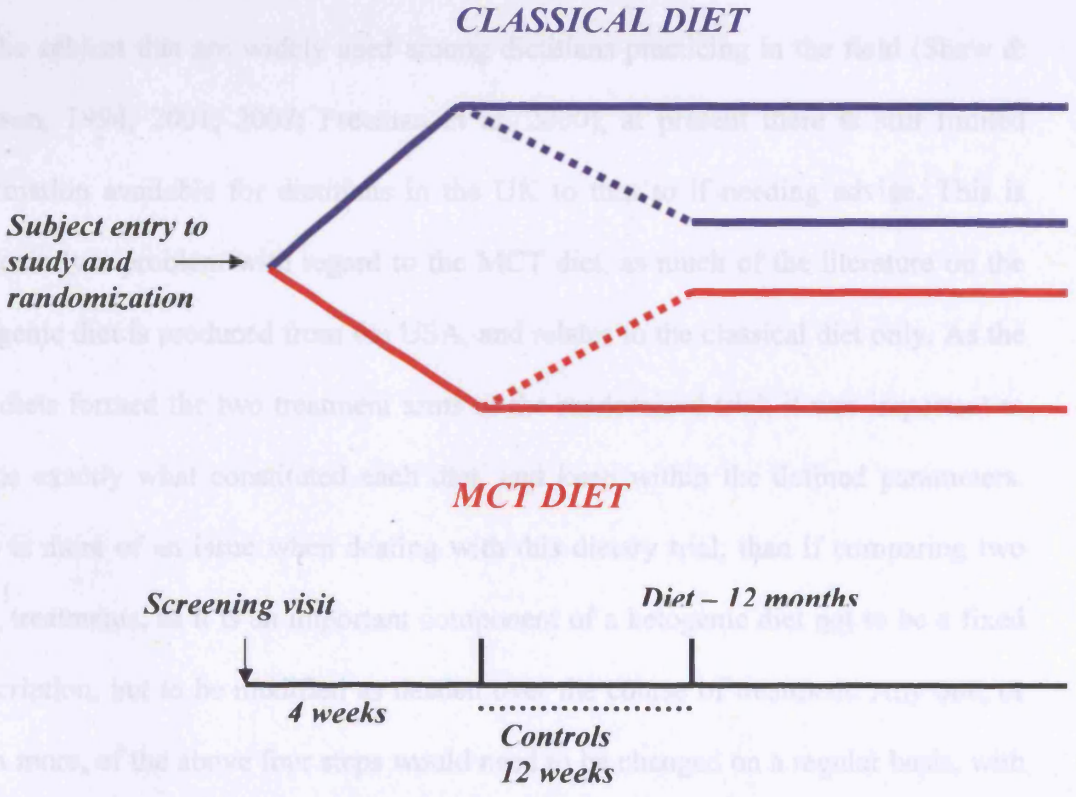
Ethical permission for the study was obtained from the ethics committees for each of the three centres involved. Children were initially seen at a screening appointment by a paediatric neurologist, paediatric dietitian and nurse. An information sheet was sent out in advance of this visit, and further details about the ketogenic diet and current study were explained at the appointment. Parents or carers of all children enrolled into the study were asked to give written consent before the child was randomized to receive either the classical or MCT ketogenic diet. Randomization was done at the time of the clinic visit by a computer program that uses the minimization method to ensure a close balance between the treatment groups for three defined age groups (2-6 years, 7-11 years, 12–16 years), and for whether the child is at the residential centre or not. This program also randomized the children to either start the diet after a 4-week baseline period of seizure records, or to start the diet after that period and an additional 3 months of seizure records, with no change in treatment; this latter group acting as their own controls for this additional pre-diet 3 month period. Subsequent to starting the diet, all children were reviewed as outpatients at 6 weeks, 3 months, 6 months and 12 months. Children were advised to follow the diet for at least 3 months, after this time the decision as to whether to

continue or not was reviewed. Table 2.1 outlines the investigations that were performed at each time point. Children were also closely monitored by telephone between clinic visits. The study design is illustrated in figure 2.1.

Table 2.1 Investigations performed at each clinic visit

Investigation	6 weeks	3months	6months	12 months
Review by Doctor	✓	✓	✓	✓
Review by Dietitian	✓	✓	✓	✓
EEG		✓	✓	✓
Blood tests		✓	✓	✓
Urine test		✓	✓	✓
Height/weight	✓	✓	✓	✓
Parental questionnaire	✓	✓	✓	✓

Figure 2.1 Study design



2.3 Calculation of a ketogenic diet – an introduction

A paediatric dietitian with specialist ketogenic diet experience (the author) calculated the classical and MCT diets. The calculation of a ketogenic diet can be divided into four steps as shown below:

- Step 1 - determining the energy prescription
- Step 2 – determining the dietary prescription by calculating amounts of the macronutrients fat, protein and carbohydrates
- Step 3 - translating the dietary prescription into meals, using recipes or food exchanges.
- Step 4 – prescribing necessary supplements to ensure nutritional requirements are met.

At the outset of this study, I wanted to be clear and consistent as to how each of these steps was to be approached for both types of diet. Although there are a couple of texts on the subject that are widely used among dietitians practicing in the field (Shaw & Lawson, 1994, 2001, 2007; Freeman et al, 2000), at present there is still limited information available for dietitians in the UK to turn to if needing advice. This is particularly a problem with regard to the MCT diet, as much of the literature on the ketogenic diet is produced from the USA, and relates to the classical diet only. As the two diets formed the two treatment arms of the randomized trial, it was important to define exactly what constituted each diet, and keep within the defined parameters. This is more of an issue when dealing with this dietary trial, than if comparing two drug treatments, as it is an important component of a ketogenic diet not to be a fixed prescription, but to be modified as needed over the course of treatment. Any one, or often more, of the above four steps would need to be changed on a regular basis, with the aim of improving seizure control, ketosis, growth, acceptance or tolerance. I

needed to define not only how the two diets were going to be initially calculated, but also the parameters within which their prescriptions could be modified if necessary, while the child still clearly remained on the treatment arm he or she had been randomized to. The process by which this was achieved for each of these four steps will be examined separately.

2.4 Determining the energy prescription

Recommendations for classical ketogenic diet calculations agree a moderate energy restriction is of benefit in ketosis and seizure control (Eaton, 1994; Freeman et al, 2000). This prescription varies according to the age of the child, however approximately 75% of the recommended intake for the child's age and ideal weight is frequently suggested. A figure of 75kcal per kg body weight has been quoted (Eaton, 1994), decreasing as the child gets older, to 40 - 50 kcal per kg by ages 11 years and older (Freeman et al, 2000). The only currently available textbook recommendation for energy prescription on the MCT diet suggests that this should be calculated using the UK recommended amount of energy for a child's age (Eaton, 1994), which is considerably more calories than would be given for a comparable classical diet. A literature review on the MCT diet suggests conflicting reports regarding energy prescriptions (see Table 2.2). It is of interest that the original paper on the two diets (Huttenlocher, 1976) did not distinguish between the classical or MCT protocol in terms of total daily energy prescription.

Table 2.2. Summary of studies reporting MCT ketogenic diet treatment

Authors	No	Age range (yrs=years, mo=months)	Energy prescription	Diet prescription	Translating into meals
Berman, 1978	18	2-17 yrs	60-75cal/kg	19% CHO, 10% protein, 11% LCT fat in foods, 60% MCT	Not stated
Clark & House, 1978	13	Not stated	RDA (UK)	60% MCT, 40% food	100kcal and 50kcal
Huttenlocher et al, 1971	12	2.5-16 yrs	RDA (USA)	19% CHO, 10% protein, 11% LCT fat in foods, 60% MCT aimed for	Protein, carbohydrate and fat exchanges
Huttenlocher et al, 1976	18	18 mo-18 yrs	'low maintenance' (75kcal/kg)-increased as needed	18% CHO, 10% protein, 12% LCT fat in foods, 60% MCT	Not stated
Mak et al, 1999	13	3 yrs – 13 yrs	110% of recommended daily requirement (Tawain)	1.5-2g protein/kg/day, < 19%CHO, MCT 65-70%, fat in food not less than 10%	Not stated
Ross et al, 1985	9	3 mo -13 yrs	'recommended total calories for age' (USA)	'Protein 1-1.5g/kg, remaining energy in 3:1 ratio of fat:CHO, with 60% of total energy as MCT'= approx 5-8% protein, 12% CHO and 80% fat (60% MCT; 20% LCT)	Not stated
Schwartz et al, 1989	55 children and 4 adults	20 under 5 yrs; 25 aged 5-10 yrs; 9 aged 11-15 yrs, and 5 aged 15-54 yrs	RDI (UK)	19% CHO, 10% protein, 11% LCT fat in foods, 60% MCT Modified diet (n=13) – 19% CHO, 10% protein, 30% MCT, 41% LCT	Protein and carbohydrate exchanges used
Sills et al, 1986	50	2-15 yrs	'assessed on individual basis by dietitan'	60% MCT aimed for	Not stated
Trauner et al, 1985	17	12mo – 13 yrs	'total calorie needs calculated' – energy intake gradually increased to approx 150% of needs (nec to prevent weight loss)	60% MCT, 15% protein, 15% CHO, 10% fat	Not stated

The problem with applying clear numeric guidelines regarding energy prescription is that it does not allow for individual variation. Energy requirements will be influenced by seizure activity, physical activity, recent growth trends, current weight and height, and any relevant medication. For this reason, all children entering the study were individually assessed. Weight and height were plotted using a computer growth package (Cole TJ, Pan. H. lmsGrowth: an Excel add-in to convert measurements to Z-scores), and any recent trends noted. A 4-day food diary was analysed on the computer for each child (Compeat Pro v5.8) to provide an estimation of pre-diet calorie intake. Initial prescription was based on an average between this pre-diet intake, and recommendations from Johns Hopkins for energy requirements on the ketogenic diet (Freeman et al, 2000), but taking into account weight and height (both current and recent trends), UK requirements (Department of Health, 1991), physical activity levels, seizure activity and medications. As no literature evidence was found for increased energy allowance on the MCT diet, no difference was made between the two diets in determining the prescription.

Modifications to energy prescriptions were needed during the course of follow-up as part of dietary fine-tuning; these were generally applied in increases or decreases of 100kcal increments, and waiting at least 2 weeks before any further changes were applied. 50kcal increments were used in children with a very low daily energy prescription, for example, the very young or non-ambulant.

2.5 Calculating the dietary prescription

Step 2 involves the calculation of a dietary prescription, based on amounts of the macronutrients fat, protein and carbohydrate. A classical ketogenic diet is based on a ratio of fat to carbohydrate and protein, generally 3:1 or 4:1. In a 3:1 diet, 87% of the

energy is provided by fat, in a 4:1 diet this increases to 90%. Fat source is long chain, usually from foods such as butter, mayonnaise, margarine, oil, cream, or a prescribable fat supplement. Protein intake is based on minimum requirements for growth (World Health Organisation, 1985; Dewey, 1996), and is generally provided by a portion of meat, fish, egg or cheese at each meal. Due to the limited carbohydrate allowance, it is difficult to include protein foods that contain additional sources of carbohydrate, such as sausages, fish fingers or milk. Starchy foods such as cereals, bread, potato or rice are generally not allowed, the main carbohydrate sources being a limited portion of vegetables or fruit.

Johns Hopkins provides an excellent formula for calculating the classical diet (Freeman et al, 2000), this is widely employed throughout the world; this formula was used to calculate all classical ketogenic diets for this study. Most children required a 4:1 ratio diet to achieve the necessary ketosis and seizure control; children who needed to lose weight and the very young only needed a 3:1 ratio. Adjustments to ketogenic ratio, made to fine tune study children on classical ketogenic diets, were done by increases or decreases in 0.5 increments, and kept within a range between 2:1 and 5:1.

When calculating the MCT ketogenic diet, the first step is to determine the percentage of total energy to be provided from the MCT fat. Although studies reported in the literature generally employ the traditional 60% energy MCT diet (see table 2.1), the author is familiar with many centres in UK that use the modified (John Radcliffe) version of 30% energy MCT. Both protocols have limitations, the former often resulting in tolerance problems; the latter a poor ketosis. The energy value of the MCT is an unresolved issue. Current European Union guidelines state that the standard conversion factor for fat of 9 kcal per gram should be used (Anonymous,

1990), however most studies on the MCT diet have used the widely accepted lower value of 8.3 kcal per gram. More recent work suggests an even lower value of 7 kcal per gram is more accurate (Ranhotra et al, 1995).

The remaining energy in the MCT diet is provided from carbohydrate, protein and long chain fat. The original diet as devised by Huttenlocher provided 10% energy as protein, 18-19% energy as carbohydrate, and the remaining 11-12% as saturated fat from foods. Other studies have used different breakdowns of macronutrient energy supply for the MCT diet, as illustrated in table 2.1, notably as low as 12% carbohydrate (Ross et al, 1985). The John Radcliffe modified diet has a remaining energy breakdown of 19% carbohydrate, 10% protein, 30% long chain fat with an additional 11% fat from foods (Schwartz et al, 1989a).

A problem for many dietitians using the MCT diet, in particular those with limited experience, is that these figures are taken as fixed values, and not fine tuned as needed to suit the individual concerned. For this current study, a starting level of 45% energy from MCT was used when calculating the MCT diets, in order to provide a balance between gastro-intestinal tolerance and adequate ketosis. This was increased up to a maximum of 60% energy MCT, or reduced to a minimum of 30% energy MCT as needed during dietary fine-tuning; generally using increments or decrements of 5% energy. The resulting increase or decrease in energy was usually balanced by a reduction or increase in the amount of long chain fat, to maintain overall calorie content of the diet. In view of the lack of updated European Union guidelines, the original value of 8.3kcal per gram MCT was used. Carbohydrate was started at 15% of energy; a figure of 18-19% energy was considered slightly too high to achieve adequate ketosis. This was reduced to a lowest value of 12% if necessary during fine-tuning. Reduction of carbohydrate to improve ketosis was only done if an increase in

MCT were not possible due to poor tolerance. Protein was usually started at 10% energy; up to 12% was needed in older non-ambulant children with very low energy requirements, in order to meet estimated protein requrements. The remaining starting energy provided from long chain fat was therefore usually 30%.

2.6 Translating the dietary prescription into meals

Having calculated a ketogenic dietary prescription, step 3 is to turn this into meals (and snacks if required) that will suit the individual child. The 4-day pre-diet food diaries gave an indication of a child's food preferences and eating patterns over the day, this was also discussed during a pre-diet telephone consultation with parents or carers, and was used as a basis for ketogenic meal plans wherever possible, within the constraints of the dietary restrictions. Many children with seizures actually have a preference for high fat foods prior to commencing the diet (Amari et al, 2007).

When administering a classical diet, the dietitian will use the dietary prescription to calculate a range of meal and snack recipes, all of which will be in the prescribed dietary ratio and exact amounts for the individual child. Parents or carers will then follow these recipes, weighing out all food, usually to the nearest one-gram increment. The conversion of a dietary prescription to recipes has traditionally involved time-consuming hand calculations, although a couple of computer calculation programs are available from the USA, using American food values. These were not appropriate for a UK based project; therefore prior to starting the study, I developed a computerized calculation program for UK ketogenic diet recipes. The development and evaluation of the program is discussed later in this chapter.

The increased carbohydrate and protein allowance on the MCT ketogenic diet means a much wider range of foods can be incorporated. This diet has traditionally

been administered by using food exchange (or choice) lists as opposed to exact meal calculations, either separate carbohydrate and protein exchanges (usually 10g and 6g respectively), or calorie exchanges (for example, 50kcal or 100kcal). Three studies reported use of exchanges; none report using exact recipe calculations (see table 2.1). Although this more flexible system makes the diet easier to calculate, there are two main problems with its use. It can cause an uneven distribution of carbohydrate, protein and fat over the day, leading to fluctuations in ketone levels, and it can lead to inaccuracy in calculations. For example, a protein intake thought to be 10% of total energy will actually be higher unless the low biological value protein provided from carbohydrate exchanges is also included, and if the energy provided from 'fat in foods' is only an estimation, it could vary greatly within a persons diet and between people. These problems with the MCT diet will be compounded in many centres by the frequent inclusion of a 'free' vegetable list, the omission of MCT from some snacks or meals, and the less accurate weighing of food exchanges (using five-gram rather than one-gram increments).

Although the impact of these problems on seizure control is undetermined, it was considered extremely important to use a tightly controlled MCT diet protocol for this current study. In comparing the efficacy and tolerability of two ketogenic diets, the use of a stricter MCT regime that was free from any of these potential problems would allow a more rigorous testing of the original idea behind the MCT diet – that using MCT to replace long chain fat increases ketosis, and so allows more carbohydrate and protein without reducing efficacy. A different approach to the exchange system was therefore devised. This used exchange lists for carbohydrate (10g), protein (6g), and long chain fat (5g). The carbohydrate exchanges provided an average of 1.5g of protein each, which was included into the calculations, and the

protein exchanges were fat-adjusted to give an average of 3g of long chain fat per exchange. When teaching parents or carers, exchanges were structured over the day by specifying numbers for each meal, with an exact amount of MCT fat to balance the carbohydrate and protein in the meal. Snacks were generally given as recipes, containing a prescribed amount of MCT. This method allowed a more careful balance of fat (both MCT and long chain) to carbohydrate and protein over the whole day, while still using a system of exchanges rather than recipes. All food was weighed to one-gram increments, and all vegetables were included in the carbohydrate calculation, and chosen from a specially designed fruit and vegetable exchange list. This list was used for both classical and MCT diets. The exchange lists for carbohydrate, protein, fat and fruit and vegetables are included with other developed dietetic resources in the appendix.

The source of MCT was traditionally MCT oil, as used by Huttenlocher et al (1971, 1976). Sills et al (1986) first reported use of an alternative MCT emulsion (Liquigen); this improved tolerance and is now used by most centres that follow an MCT ketogenic diet protocol. For the current study, Liquigen was used as the initial MCT source; this can be mixed into milk for drinks or cooking, and also used in recipes. Finding acceptable ways to incorporate MCT into the diet is the key to good compliance; children who refused milk-based drinks often needed an additional prescription for MCT oil, as this can be used in smaller volumes for cooking.

Children who are unable to take the ketogenic diet orally can safely have their diet prescription translated into a suitable enteral feed, to be given either via gastrostomy or naso-gastric tube. This has been shown to be safe and effective in a small study (Hosain et al, 2004). Prescribable dietary products can be used to implement both classical and MCT diets. In the current study, a couple of extra

products were made available for use from Scientific Hospital Supplies. Ketocal, a complete 4:1 ratio powdered formula, was used as the base product for all classical diet enteral feeds. Ketoflex, a protein, vitamin, mineral and trace element source, was used for the MCT diet enteral feeds, combined with Liquigen and carbohydrate and long chain fat sources. Since study completion, Ketocal has been made available on prescription in the UK.

2.7 Prescribing necessary supplements

Step 4 involves prescribing necessary supplements to ensure a child's ketogenic diet is nutritionally adequate. After reviewing the available products and nutritional requirements of each age group, a supplementation protocol was drawn up for the study (see Table 2.3) There are no UK published guidelines on supplementing ketogenic diets, however this protocol is similar to that used by most UK centres practising the diet, with the exception of the additional magnesium supplementation on the classical diet, and essential fatty acid supplementation on the MCT diet. A magnesium supplement was considered necessary in view of the dietary restrictions, as the amount provided by Forceval Junior (paediatric vitamin and mineral supplement, see Table 2.3) is well below requirements. Magnesium deficiency is unlikely to be a problem on the MCT diet due to increased cereal and vegetable content. Essential long chain fatty acid deficiency is unlikely, but could be a risk in children on the MCT diet receiving 60% energy from MCT, due to the very small amount of long chain fat that would be allowed. Enterally fed children had full supplementation provided by the Ketocal or Ketoflex product used in their feed.

Table 2.3. Supplements used for classical and MCT ketogenic diets

Supplement	Classical Diet	MCT Diet
General	Forceval Junior – 1 capsule daily ages 2-10 years 2 capsules daily ages 11-16 years	
Calcium	Sandocal 400 – 1 X 10mmol tablet daily	Requirements depend on dietary intake. ½ - 1 X Sandocal 400 daily if needed
Other	Magnesium glycerophosphate – ½ - 1 X 4mmol tablet daily (commenced after 3 months on diet)	2ml walnut oil daily as essential fatty acid source (commenced after 3 months on diet)

2.8 Initiating the ketogenic diets

On commencing this study, a protocol of outpatient initiation, without a fast or fluid restriction, was established. All families attended the hospital for a full initiation day of outpatient education prior to commencing the ketogenic diet. At this initiation visit, baseline haematology and biochemistry blood tests were done, and urine samples were taken to check for haematuria. All children on topiramate had a baseline renal ultrasound performed to exclude pre-diet renal calculi. Diets were started at the beginning of a week, to avoid complications occurring over the weekend, and during the first two weeks on the diet families had daily telephone contact with an experienced ketogenic dietitian or nurse (often more frequently for the first few days). On-going regular telephone contact was maintained as needed.

Both classical and MCT ketogenic diets were initiated using a gradual step-wise protocol. Classical diet children were commenced on full calories at a 2:1 ratio for the first 2-3 days. This was achieved by adding a prescribed amount of extra orange juice to 4:1 ratio recipes at each meal and snack; this was then slowly reduced to increase the ratio to 3:1, as tolerated. After a further few days, the orange juice was

stopped, leaving the child on a 4:1 ratio diet, if tolerated. All incremental orange juice reductions were made after discussion with the dietitian or nurse, and with close monitoring of ketone levels and tolerance. MCT diet children were commenced on the full prescription of carbohydrate, protein and fat from foods, but with a very small amount of MCT. The MCT was built up to the full prescription in daily increments over 10 days, again depending on ketone levels and tolerance. Fluids were not restricted on either diet, however children who drank large amounts were advised to keep to the recommended daily amounts for their age group.

2.9 Development and evaluation of EKM

Prior to starting the study, the need for a computer calculation program relevant to the UK was identified, to allow the highly prescriptive and time-consuming ketogenic diet recipe calculations to be performed quickly and easily. No such programs were currently available for use with UK food values, and the aim of such a program would be to reduce the burden of time for dietitians involved in this area of work.

The original idea was based on Microsoft Excel software, using a simple spreadsheet with inputted food values. This idea was then used to design a stand-alone program, not dependant on Excel, working in conjunction with a software engineer (MicroMan2000 Ltd), who had previously designed a well-used dietetic feed calculation program, Electronic Dietetic Manager (EDM). The new ketogenic diet recipe calculation program was named Electronic Ketogenic Manager (EKM). Once the dietitian has calculated a dietary prescription, EKM enables recipes to quickly be planned and adapted, using McCance & Widdowson 6th Edition Food Composition data. Parents can also use it to plan meals, based on a prescription given to them by

the dietitian. EKM was designed to be available free, and is obtained by download from the internet. There were initial concerns about such a program being misused by parents without any dietetic or medical supervision. In order to be sure that it is used appropriately it was decided to only allow parents to download after email permission has been obtained from the dietitian managing their diet. It is of note that the programs of similar nature produced in the USA are available on the internet and do not include any such supervisory checks. The timescale for program development is given in table 2.4.

Table 2.4 Timetable for development of EKM

Time	Action
December 2001 – February 2002	Design of simple ketogenic diet calculation spreadsheet using Microsoft Excel software, first used February 2002, used for all study diets calculated until February 2004
February 2004	First meeting with software engineer (MicroMan2000 Ltd) regarding development of a stand-alone program
February - September 2004	Program design and development, used alongside Excel version for study diets. Licensing agreement with Institute of Chemistry, to enable a one-off purchase of McCance & Widdowson 6th Edition Food Composition data; this enabled program to be available free to users.
September 2004	Draft windows version of EKM ready. Initial evaluation by 2 dietitians and 2 parents after ½ day training session.
11th November 2004	Official release of EKM at ketogenic diet conference (Institute of Child Health)

In February 2005, 3 months after program launch, an initial questionnaire was sent out by email to the first users of EKM (4 dietitians and 3 parents), all of who had been using the program for at least one month. This questionnaire asked about ease of use, whether there had been any problems, how the program compared with their previous method of meal planning, and whether they would use it on a regular basis to calculate ketogenic diet meals.

Six of the 7 respondents (86%) reported finding EKM easy or very easy to use, one dietitian initially found it more difficult. When asked about any problems, 3 dietitians reported having some computer compatibility problems that resolved with help; the other 4 respondents had no problems. All respondents said that the program was much better than their previous methods of calculating recipes, and that they would use the program on a regular basis; the dietitians finding that it was much easier than hand calculating ketogenic recipes, and the parents enjoying the freedom of calculating their own meals, working alongside their dietitian. These initial pilot questionnaire results were encouraging, although the survey was limited by small sample size. Users generally found it easy to use and it reduced the time taken to calculate a ketogenic diet.

A survey of EKM users in March 2006 showed that by this time 104 people had downloaded the program for use: 51 dietitians and 53 parents. At a recent international ketogenic diet conference in November 2007, many countries other than the UK reported using EKM. The on-going aim is that more dietitians working in this area will use EKM as a resource; by freeing up dietetic time this will hopefully allow more children with severe epilepsy to try this treatment.

2.10 Development of other dietetic resources

A range of other written information was produced to give to parents or carers on the initial education visit. This included a parents illness information sheet, information on how to measure ketones, and separate information sheets for classical and MCT diets, including example recipe ideas. This written information is included in the appendix to chapter 2.

APPENDIX – DIETETIC RESOURCES

1. Fruit and vegetable exchange lists
2. Carbohydrate, protein and fat exchange lists
3. Classical and MCT diet general information sheets
4. Illness information sheet
5. Measuring ketones information

Exchange Lists for Fruit and Vegetables

FRUIT

Weights are given for raw fruit (not dried), fruit stewed without sugar, or fruit canned in natural juice. As there are individual variations in the carbohydrate content of the different fruits within a group, try and vary choices. If you find that one type of fruit is being used very regularly then discuss this with the dietitian as the overall ratio of your diet may need to be checked.

10% fruit - these contain an average of 10g carbohydrate per 100g. Use the amount prescribed for each meal:

Apples
Apricots
Cherries
Damsons
Peaches
Pears
Pineapple
Canned fruit cocktail (in natural juice)
Oranges, including mandarin, satsuma and tangerine
Kiwi fruit
Nectarines
Paw-paw
Plums
Watermelon

Lower Carbohydrate fruits (approx 6 ½ %) - these contain an average of 6 ½ g carbohydrate per 100g. Use 1 ½ times the amount prescribed for each meal:

Blackberries
Blackcurrants
Blueberries
Grapefruit
Lemons
Gooseberries
Loganberries
Melon - canteloupe, honeydew, galia
Raspberries
Redcurrants
Strawberries
Cranberries

Higher carbohydrate fruits (approx 15%) - these contain an average of 15g carbohydrate per 100g. Use 2/3 of the amount of fruit prescribed for each meal:

Mango
Grapes
Lychees

Banana - contains approx 23g carbohydrate per 100g. Use 1/3 of the amount of fruit prescribed for each meal.

VEGETABLES

Weights are given for raw (R) or cooked (C) vegetables. 'Cooked' refers to boiling or steaming. Try and vary choices due to individual variations in carbohydrate and protein content within a group. If one type of vegetable is being used at most meals discuss this with the dietitian to enable checking of the overall diet ratio.

Group 1 vegetables - these contain moderate amounts of carbohydrate and protein. Use the amount prescribed for each meal.

Beetroot - R
Sprouts - R or C
Onion - R
Turnip - R
Mangetout - R or C
Beansprouts - R
Okra – R or C
Cauliflower – R
Carrots - R or C
French beans - R or C
Swede - R
Red or yellow pepper - R or C
Cabbage/spring greens - R
Butternut squash – R or C
Broccoli – R

Group 2 vegetables - these contain lower amounts of carbohydrate and protein. Use twice the amount of vegetable prescribed for each meal.

Asparagus - R or C
Runner beans - R or C
Cabbage/spring greens - C
Courgette - R or C
Leeks - R or C
Marrow - R
Radish - R
Spring onion - R
Tomato - R or canned
Watercress - R
Celeriac – R or C
Aubergine - R
Broccoli - C
Cauliflower - C
Green pepper - R or C
Turnip - C
Pumpkin - R or C
Spinach - R or C
Swede - C
Curly kale – R or C
Chicory - R
Fennel - R

Group 3 vegetables - these are very low in carbohydrate. Use four times the amount of vegetable prescribed for each meal.

Celery - R or C
Cucumber - R
Lettuce - R
Mustard & cress - R
Marrow - C
Mushroom – R
Fennel - C
Rhubarb - although actually a fruit, this is very low in carbohydrate, so can be used in group 3 vegetable amounts. It may be particularly useful if your child is constipated.

Other vegetables

There are a few other vegetables that are much higher in carbohydrate and/or protein, so cannot be included in the exchange lists. These include potato, baked beans, peas, yam, plantain and parsnip. Small amounts of these vegetables can be calculated into the diet separately by the dietitian if necessary.

10g Carbohydrate exchanges for MCT ketogenic diet

Rice and pasta
12g rice (dry weight)
33g boiled rice
13g pasta or noodles (dry weight)
50g boiled pasta

Breads and crackers
24g wholemeal bread
22g white bread
18g white French stick or pitta bread
21g granary bread
23g chapatti (without fat)
20g white burger buns
23g croissants or muffins
17g hot cross buns
23g Scotch pancakes
19g scones or teacakes
14g rye crispbread
15g cream crackers

Breakfast cereals
21g All Bran
14g Branflakes
14g Fruit and fibre
11g Cornflakes
15g Puffed wheat
15g Ready brek
11g Rice krispies
14g Shredded wheat
13g Shreddies
13g Weetabix
13g porridge oats (dry weight)

Baking
13g flour (plain/self-raising)
11g cornflour
17g pizza base eg. Sainsbury's thin and crispy (ready to cook)

Miscellaneous
70g tinned spaghetti in tomato sauce
170g tinned tomato soup
100g tinned vegetable soup

Snacks
18g cheddars
16g twiglets
17g tortilla chips or wheat crunchies
19g potato crisps
13g ice cream cup cornets

High carbohydrate vegetables (raw or cooked weight)
58g potato– without skin
30g chips
39g roast potato
28g yam
35g plantain
38g sweetcorn, canned
80g parsnip

Fruits
150g of melon, grapefruit, raspberries, strawberries, loganberries, blackberries, blackcurrants or rhubarb

100g of apple, apricot (not dried), cherries, kiwi, orange, tangerine, satsuma, mandarins (including tinned) pear (including tinned), peach (including tinned), plums, pineapple, nectarine.

65g of grapes, mango, gooseberries fruit cocktail tinned in juice, pineapple tinned in juice

43g of banana

6g Protein exchanges for MCT ketogenic diet (fat-adjusted)

Fish

22g tuna, tinned in oil
26g boiled prawns with an extra 3g oil or 4g butter, margarine or mayonnaise
10g dried prawns with an extra 3g oil or 4g butter, margarine or mayonnaise
30g white fish with an extra 3g oil or 4g butter, margarine or mayonnaise (eg. cod, coley, plaice, haddock, halibut, whiting)
30g smoked mackerel
35g pilchards tinned in tomato sauce
30g salmon (raw or steamed weight)
24g smoked salmon with an extra 2g oil or 3g butter, margarine or mayonnaise
25g tinned salmon
25g sardines, tinned in oil
33g sardines, tinned in tomato sauce

Meat

26g raw beef meat
20g grilled beef steak
20g roast beef
30g raw lamb meat
20g grilled lamb steak or chops
21g roast lamb
28g raw pork meat with an extra 2g oil or 3g butter, margarine or mayonnaise
19g roast pork with an extra 2g oil or 3g butter, margarine or mayonnaise
30g raw mince (either beef, lamb or pork)
27g raw chicken meat or turkey meat with an extra 3g oil or 4g butter, margarine or mayonnaise
19g grilled chicken breast with an extra 3g oil or 4g butter, margarine or mayonnaise
20g roast chicken breast with an extra 2g oil or 3g butter, margarine or mayonnaise
19g roast turkey with an extra 2g oil or 3g butter, margarine or mayonnaise
30g raw liver
36g raw bacon
25g grilled bacon
25g boiled gammon
33g ham with an extra 2g oil or 3g butter, margarine or mayonnaise
23g corned beef
29g salami

Cheese
24g cheddar
47g cottage cheese (not low fat)
23g Edam
30g brie
26g stilton

Other
1 small egg (approx 50g)
43g quorn

Foods that give both carbohydrate and protein exchanges

- 70g fruit fromage frais = 1 carbohydrate exchange and ½ protein exchange
- 120g Muller Light yoghurt = 1 carbohydrate exchange and 1 protein exchange
- 60g baked beans with an extra 3g oil or 4g butter, margarine or mayonnaise = 1 carbohydrate exchange and ½ protein exchange
- 60g fish cakes OR fish fingers = 1 carbohydrate exchange and 1 protein exchange
- 40g sausage = ½ carbohydrate exchange and 1 protein exchange

5g Fat exchanges for MCT ketogenic diet

6g butter -	any type of butter, eg, Anchor, Country Life, supermarkets own brand
5g oil -	a vegetable oil, such as olive or sunflower is recommended
6g mayonnaise -	Hellmans (jar), or alternative full fat
8g margarine -	For example, Flora. Not low fat spreads.
10g double cream -	any type, including UHT.

20g Philadelphia full fat cream cheese – maximum once daily as a fat exchange

12g mascarpone cheese – maximum once daily as a fat exchange

30g avocado pear - maximum once daily as a fat exchange

7g walnuts, macadamia nuts or brazil nuts - maximum once daily as a fat exchange

9g almonds or peanuts - maximum once daily as a fat exchange

The MCT Ketogenic Diet

This diet contains a prescribed amount of medium chain triglyceride (MCT). This is a special type of fat, which helps the body produce ketones. It is usually given in the form of an emulsion called Liquigen, however MCT oil can also be used if necessary. These products are available on prescription for use in this diet.
The diet is also made up of a prescribed amount of other fat, protein and carbohydrate. The daily amounts of these nutrients have been carefully calculated on an individual basis, and it is therefore important that the recipes are followed exactly.
The MCT ketogenic diet allows adequate protein to meet requirements, however the carbohydrate content is lower than normal diets. The carbohydrate in the diet will be provided by starchy foods only, as sugar and sugary foods are not allowed on this diet.

You have been given a choice of meal recipes (see separate sheets) for initial use, based on your child's food preferences. The dietitian can adapt these and add new foods as needed, however, all changes should be discussed with her, as they will need to be carefully calculated into the diet.
Food should be weighed to the nearest 1g, as specified in the recipes. 1g of liquigen or milk is the same as 1ml, however you will probably find it easier to weigh rather than measure these liquids.
All meals and snacks will contain a significant proportion of oil, butter, mayonnaise or double cream, or a combination of these fat sources. The recipes do not specify which of these should be used, however have been based on the following products:

- Oil - a vegetable oil, such as olive or sunflower is recommended
- Butter - any type of butter, eg, Anchor, Country Life, supermarkets own brand.
- Margarine - this is slightly lower in fat than butter and may be less palatable in large quantities, however, provides a healthier balance of fatty acids. The type used will be specified in the recipes.
- Mayonnaise - Hellmans (jar), or alternative full fat.
- Double cream - any type.

All meals and snacks will also contain a prescribed amount of Liquigen. This can be included in the diet by mixing with milk (for drinks and on cereal), using in cooking, or making up as a sugar-free jelly. The amounts of milk or other ingredients needed to combine with the liquigen are carefully calculated, and included in your recipes.
Once a bottle of liquigen has been opened, it should be kept in the refrigerator.

Free foods

There are no free foods on this diet, except as specified in the list below.

Drinks Tea and coffee (no milk or sugar, acceptable sweeteners only)
Water, including mineral. Flavoured waters can be used if only contain a trace of carbohydrate, eg. Tesco still flavoured mineral waters.
Diet fizzy drinks - check that carbohydrate content is less than 0.1g/100ml

Sugar free squash - check the label as some low sugar products still contain significant amounts of carbohydrate. Aim for a carbohydrate content of 0.6g or under per 100ml of undiluted drink, or 0.1g per 100ml diluted drink.
(different manufacturers choose to label drinks in different ways)
Some suggestions are:

- Sainsbury's - no added sugar whole orange, orange, lemon and pineapple, lemon, lemon & lime or blackcurrant drinks. Low price no added sugar orange drink *
- Tesco's - low sugar whole lemon squash, whole grapefruit squash, or whole orange squash. Value low calorie apple and blackcurrant, lemon or orange drinks*
- Safeway no added sugar lemon, orange or strawberry drinks. Safeway savers no added sugar apple and blackcurrant or orange drinks.*
- Asda no added sugar orange and lemon drinks. Asda Smartprice no added sugar orange, lemon or apple & blackcurrant drinks.*

*Information correct at Dec 2003 – do check label again in case of changes.

Sweeteners Saccharin is the best choice eg. Sweetex or hermesetas tablets. Avoid sweeteners containing sucrose, fructose, glucose, lactose, sortbitol or maltodextrin. Aspartame can be used in moderation. Avoid powdered sweeteners, eg. Candarel, as these contain significant amounts of maltodextrins.

Flavourings Salt, pepper, herbs and spices.
Pure food essences and colourings

Vitamin and mineral supplementation

This diet is not nutritionally complete. A supplement will need to be taken daily - please see details on your diet sheet.

Medicines and toothpaste

These should be sugar-free if possible. Check with your pharmacy, doctor or the ketogenic diet team if you are uncertain.
Toothpaste should be sugar free if possible. Suitable types are Colgate baking soda toothpaste and Arm & Hammer baking soda toothpaste (available in supermarkets).

Initiating the diet

Liquigen should be introduced into the diet slowly - please see the plan on your diet sheet for building up the amount.

The Classical Ketogenic Diet

The ketogenic diet is very high in fat, and low in carbohydrate. The carbohydrate will be provided by a limited amount of starchy foods only, such as fruit and vegetables, as sugar and sugary foods are not allowed on this diet. The diet is also low in protein, however provides an adequate amount for growth. The daily amounts of these nutrients have been carefully calculated on an individual basis, and it is therefore important that the recipes are followed exactly.

You have been given a choice of meal recipes (see separate sheet) for initial use, based on your child's food preferences. The dietitian can adapt these and add new meals as needed, however, all changes should be discussed with her, as they will need to be carefully calculated into the diet. Food should be weighed to the nearest 1g, as specified in the recipes.

All meals will contain a high proportion of oil, butter, margarine, mayonnaise or double cream, or a combination of these fat sources. The recipes do not specify which of these should be used, however have been based on the following products:

- Oil - a vegetable oil, such as olive or sunflower is recommended
- Butter - any type of butter, eg, Anchor, Country Life, supermarkets own brand.
- Margarine - this is slightly lower in fat than butter and may be less palatable in large quantities, however, provides a healthier balance of fatty acids. The type used will be specified in the recipes if wanted.
- Mayonnaise - Hellmans (jar), or alternative full fat.
- Double cream - any type.

Free foods

There are no free foods on this diet, except as specified in the list below.

Drinks

Tea and Coffee (no milk or sugar, acceptable sweeteners only)
Water, including mineral. Flavoured waters can be used if only contain a trace of carbohydrate, eg. Tesco still flavoured mineral waters.
Diet fizzy drinks - check carbohydrate content is below 0.1g/100ml
Sugar free squash - check the label as some low sugar products still contain significant amounts of carbohydrate. Aim for a carbohydrate content of 0.6g or under per 100ml of undiluted drink, or 0.1g per 100ml diluted drink.
(different manufacturers choose to label drinks in different ways)
Some suggestions are:

- Sainsbury's - no added sugar whole orange, orange, lemon and pineapple, lemon, lemon & lime or blackcurrant drinks. Low price no added sugar orange drink *

- Tesco's - low sugar whole lemon squash, whole grapefruit squash, or whole orange squash. Value low calorie apple and blackcurrant, lemon or orange drinks*
- Safeway no added sugar lemon, orange or strawberry drinks. Safeway savers no added sugar apple and blackcurrant or orange drinks.*
- Asda no added sugar orange and lemon drinks. Asda Smartprice no added sugar orange, lemon or apple & blackcurrant drinks.*
- Information correct at Dec 2003 – do check label again in case of changes.

Sweeteners Saccharin is the best choice eg. Sweetex or hermesetas tablets. Avoid sweeteners containing sucrose, fructose, glucose, lactose, sortbitol or maltodextrin. Aspartame can be used in moderation. Avoid powdered sweeteners, eg. Candarel, as these contain significant amounts of maltodextrins.

Flavourings Salt, pepper, herbs and spices.
Pure food essences and colourings

Vitamin and mineral supplementation

This diet is not nutritionally complete. A supplement will need to be taken daily, as specified on your diet sheet.

Medicines and toothpaste

These should be sugar-free if possible. Check with your pharmacy, doctor or the ketogenic diet team if you are uncertain.
Toothpaste should be sugar free if possible. Suitable types are Colgate baking soda toothpaste and Arm & Hammer baking soda toothpaste (available in supermarkets).

How to manage illness while on the ketogenic diet

You may notice that ketone levels drop if your child becomes unwell. This is quite common, and caused by a combination of factors, such as the infection itself and decreased physical activity. Although we would aim to maintain ketosis during illness if possible, it is far more important for your child to get well again.
At times of illness, if you are concerned about you child, it is important to contact your local doctor or ketogenic diet specialists. However the following guidelines give some general advice on how to manage illness while your child is following a ketogenic diet.

Vomiting or diarrhoea

- Stop the diet, and use Dioralyte until vomiting has settled. It is extremely important to maintain an adequate fluid intake at this time, so drinks should be offered frequently as tolerated. Clear sugar-free liquids such as water, sugar-free fizzy drinks and sugar-free squash could be used instead if preferred in older children, however if the symptoms continue for over 24 hours, Dioralyte should be used, as this will replenish the body's electrolyte levels. If your child is being fed by gastrostomy or nasogastric ketogenic feeds, these should be stopped, and Dioralyte or water used in place of the feeds, ensuring an adequate fluid intake.
- Watch carefully for signs of low blood sugar and /or excess ketosis during this time. If there is no improvement in 24 hours, your local doctor should be contacted.
- When your child has stopped vomiting, re-introduce the diet. This should be done slowly. If your child is not able to take solid foods, the ketogenic milkshake recipe can be offered in small sips throughout the day. This may need to be initially diluted with water or dioralyte if there are problems with tolerance due to continued diarrhoea. The amount of milkshake given can slowly be increased, and then replaced with meals once appetite has returned. It does not matter if the correct amount of milkshake for the day cannot initially be completed, however during this time of building the diet back to normal it is essential to maintain an adequate fluid intake with other sugar-free drinks.
- When reintroducing meals, start with half the usual amounts for the first day or two. If your child is unable to complete meals, mix the meal constituents together, so that the food eaten is in the correct ratio of fat to protein and carbohydrate. If your child is unable to tolerate the full-fat meals due to continued diarrhoea or vomiting, it may be necessary to reduce the fat in the diet for a couple of days. Use half the prescribed amount of cream, butter, oil and/or mayonnaise at each meal for a day, and slowly increase this back to normal over the next couple of days as tolerated. If you are using Liquigen (MCT diet only), the amount used may also need to be reduced by half, and then built back up to full strength over 2-3 days. If diarrhoea is a continuing problem, the Liquigen may need to be introduced at a quarter strength and built up to the full amount over 4-5 days - this can be discussed with the dietitian.
- When reintroducing gastrostomy or nasogastric ketogenic feeds, initially use half strength for 24-48 hours, then gradually build up to full strength as tolerated over a few days.

Fever

- Use sugar free paracetamol or suppositories at the correct dose for your child.
- Maintain an adequate fluid intake by offering sugar free fluids without restriction. If your child will eat as usual, then the diet can be maintained. However, you may prefer to use the milkshake recipe - this can be sipped throughout the day.
- It is important to contact your local doctor, as you would normally, if you are worried about your child's health.
- Any other medication, such as antibiotics, should be sugar-free if possible.

Constipation

- Discuss this with your dietitian as some dietary changes may be possible
- Lactulose can be used as a stool softener and so can Fybogel. These products have very limited absorption into the body, so are unlikely to interfere with the diet.

Seizures

- If your child is unwell with worsening of seizures, check the ketones in the urine and contact your local paediatric team
- Emergency treatment can be given as normal, eg. rectal diazepam
- If taken to hospital **a glucose infusion should be avoided** (unless in exceptional circumstances - see below). Your child can have normal saline and other types of infusion. The nurses will monitor your child's blood sugar.

Low blood sugar

Many children on the diet have lower blood sugars than they would on normal diets. This is not a problem unless symptoms develop. Symptoms of low blood sugar include sweating, becoming cold and clammy, jittery, confused or aggressive. This is rare, but if they do occur, should be treated immediately by giving a drink that contains carbohydrate, such as a sugar containing (non-diet) fizzy drink or fresh fruit juice. Start with 1 - 2 tablespoons. However, if these symptoms do develop, you should also contact your local doctor, as it will be important to monitor blood glucose levels and provide further treatment. If hospital admission is needed, a glucose infusion may be required.

Excess ketosis

Occasionally ketone levels can become too high. This may occur after a change in the diet, or during illness. The signs of this are rapid, panting breathing, increased heart rate, facial flushing, irritability, vomiting and unexpected lethargy.
If your child seems to be showing these symptoms, give 1 - 2 tablespoons of fresh fruit juice or a sugar-containing fizzy drink. If the symptoms have not improved after 15-20 minutes, this should be repeated, and your local doctor contacted immediately. It may be necessary to alter the diet ratio if ketone levels are persistently excessive.

If you are very worried about your child's health, phone your local doctor or call for an ambulance.

Instructions for ketone measurement with Ketostix

Ketones need to be measured morning and evening, at roughly the same times each day.

What you will need;
-Good lighting in the room.
-A bottle of test strips-Ketostix.
-A watch that measures seconds.
-A clean container or cotton wool balls to collect urine.

Testing urine
1. Collect urine in a clean, dry container.
2. Remove one test strip from the bottle and replace the lid.
3. Dip the test strip into the urine (or stream of urine) and remove immediately.
4. Remove excess urine on the test strip by shaking.
5. Wait 15 seconds and read the test strip by comparing with the colour chart.
6. Record result.

Testing ketones from nappies
1. Place a cotton wool ball in the nappy prior to the time of testing.
2. When the nappy is wet remove the cotton wool.
3. Squeeze the cotton wool onto the test strip, so that the urine makes the test strip wet.
4. Wait 15 seconds and read the test strip.
5. Record result.

We are aiming for large levels of ketones (8 -16 mmols/L).
However levels will vary depending on the dilution of the urine.

CHAPTER 3

EFFICACY OF THE KETOGENIC DIET

Contents

3.1 Introduction

Efficacy of an anti-epileptic treatment will be assessed by its ability to produce seizure freedom, or a reduction in seizure frequency and/or severity. This can be done by using records of seizure numbers, by using an additional graded system for records of seizure severity, by assessing the EEG, and by monitoring anti-epileptic medication use, both regular and emergency. A widely accepted measure of an efficacious anti-epileptic treatment is one that reduces seizure frequency by more than 50%. Previous ketogenic diet studies in children have used percentage response rates to present results, based on records of actual seizure numbers, with categories of seizure free, greater than 90% reduction and greater than 50% reduction. Studies are summarized in Table 3.1.

Study & location	No	Ages (yrs)	Diet type	Seizure free	>90% decrease	> 50% decrease
Berman, 1978 (USA)	18	2-17	MCT	1/18 (6%)	Not stated	6/18 (33%)
Coppola et al, 2002 (Italy)	56	1-23	Classical 4:1	Not stated	Not stated	37.5% at 3 mo 26.8% at 6 mo 17.9% at 12 mo
DiMario & Holland, 2002 (USA)	24	1-15	Not stated	4/24 (17%) at 6 mo 4/24 (17% at 12 mo	Not stated Not stated	13/24 (54%) at 6 mo 7/24 (29%) at 12 mo
Freeman et al, 1998 (USA)	150	1-16	Classical 3:1 – 4:1	4/150 (3%) at 3 mo 5/150 (5%) at 6 mo 11/150 (7%) at 12mo	50/150 (33%) at 3 mo 48/150 (32%) at 6 mo 41/150 (27%) at 12 mo	89/150 (60%) at 3 mo 77/150 (51%) at 6 mo 75/150 (50%) at 12 mo
Hassan et al, 1999 (Canada)	52	Not stated mean 5.5	Classical 4:1(49) Modified MCT (3)	6/52 (11.5%)	Not stated	35/52 (67.3%)
Hopkins & Lynch, 1970 (Australia)	34	1-13	Classical 3:1	3/34 (8.8%)	Not stated	Not stated
Huttenlocher et al, 1971 (USA)	12	2.5-16	MCT	4/12 (33%)	Not stated	Not stated
Huttenlocher, 1976 (USA)	18	1.5-18	MCT	4/18 (22%)	10/18 (56%)	16/18 (89%)
Janaki, 1976 (India)	15	0-30	Classical 4:1	3/15 (20%)	Not stated	15/15 (100%)
Kankirawatana et al, 2001 (Thailand)	35	0.2-13	Classical 4:1	5/35 (14%) at 3 mo 4/35 (11%) at 6 mo 3/35 (9%) at 12 mo	15/35 (43%) at 3 mo 12/35 (34%) at 6 mo 8/35 (23%) at 12 mo	17/35 (49%) at 3 mo 15/35 (43%) at 6 mo 10/35 (29%) at 12 mo
Kang et al, 2005 (Korea)	199	0.5-17.5	Classical 4:1	70/199 (35%) at 3 mo 66/199 (33%) at 6 mo 50/199 (25%) at 12 mo	Not stated	123/199 (62%) at 3 mo 115/199 (58%) at 6 mo 82/199 (41%) at 12 mo
Katyal et al, 2000 (USA)	48	Not stated	Classical 3:1 – 5:1	Not stated	16/48 (33%)	30/48 (63%) at 45 days
Kinsman et al, 1992 (USA)	58	1-19.6	Classical 4:1	Not stated	17/58 (29%)	22/58 (38%)
Mackay et al, 2005 (Australia)	26	2.3-13.2	Classical, 3:1-4.2:1	4/26 (15%)	5/26 (19%)	7/26 at 3mo (27%) 4/26 at 6 mo (15%) 8/26 at 12 mo (31%)
Mak et al, 1999 (Taiwan)	13	3-13	MCT	None	5/13 (38%)	7/13 (54%)
Maydell et al, 1999 (USA)	143	0.3-9	Classical 4:1	21/143 (15%) at 3 mo 24/143 (17%) at 6 mo 23/143 (16%) at 12 mo	43/143 (30%) at 3 mo 41/143 (29%) at 6 mo 38/143 (27%) at 12 mo	59/143 (41%) at 3 mo 60/143 (42%) at 6 mo 54/143 (38%) at 12 mo
Ross et al, 1985 (USA)	9	0.25-13	MCT	2/9 (22%) at 10 weeks	Not stated	6/9 (66%) at 10 weeks
Schwartz et al, 1989a (UK)	59	<5 - >15	Classical 4:1 (15), MCT (22), modified MCT (13), Mixed (9)	Not stated	26/63 studies on 55 children (41%)	51/63 studies on 55 children (81%)
Sills et al, 1986 (UK)	50	2-15	MCT	8/50 (16%)	12/50 (24%)	22/50 (44%)
Trauner, 1985 (USA)	17	1-13	MCT	5/17 (29%)	Not stated	10/17 (59%)
Vining et al, 1998 (USA multicentre)	51	1-8	Classical 4:1	6/51 (12%) at 3 mo 6/51 (12%) at 6 mo 5/51 (10%) at 12 mo	13/51 (25%) at 3 mo 15/51 (29%) at 6 mo 11/51 (22%) at 12 mo	28/51 (54%) at 3 mo 27/51 (53%) at 6 mo 20/51 (40%) at 12 mo

Table 3.1 Efficacy of the ketogenic diet – a review of the literature

When interpreting this table, it is important to note that the values for proportions that fall into each of the three categories of seizure free, greater than 90% reduction, and greater than 50% reduction, are given as a percentage of the number of children starting the diet, not as a percentage of those who were still on the diet at each time point. Authors vary in their choice of denominator; standardization for this table allows more accurate comparisons between studies. It must also be noted that the category of greater than 90% reduction will include the seizure free children, and the greater than 50% reduction category will include the seizure free and greater than 90% reduction group. Some studies do not state how long individuals were on the diet when results were reported. Where possible, the table gives results after 3, 6 and 12 months on the diet. The majority of studies reported use of the classical diet, those using the MCT version tended to have considerably smaller sample sizes.

Despite the number of studies reporting successful use of the ketogenic diet, there are concerns about the quality of the evidence base to support its claims of efficacy. The studies in Table 3.1 are all based on clinical series of patients, with either retrospective analysis of data or assessment of outcomes, or designed as prospective observational clinical trials; none were randomized or controlled. There have also been no randomized trials comparing the two diet protocols, despite frequent anecdotal claims that the classical diet may be more efficacious. Recent ILAE treatment guidelines for evidence-based analysis of anti-epileptic drug efficacy (Glauser et al, 2006) rate studies into four classes of evidence, based on criteria adapted from the American Academy of Neurology (Edlund et al, 2004) scoring systems. A class 1 efficacy study will be a randomized controlled trial, in a representative population, with a primary efficacy outcome, $\geq$ 48 week treatment duration, $\geq$ 24 weeks of efficacy data, a double blind design, and no forced study exit

due to treatment-emergent seizures. Appropriate statistical analysis must be applied, and either superiority demonstrated, or the study must have a sample size sufficient to show non-inferiority of no worse than a 20% relative difference in efficacy. A class II study will meet all the above criteria except with treatment duration of $\geq$ 24 weeks but < 48 weeks, and no demonstration of superiority, with a sample size allowing non-inferiority with a 21-30% difference in efficacy to be shown. A class III study will be a randomized controlled trial not meeting the above two criteria, and a class IV study will provide evidence from non-randomized, prospective, controlled or uncontrolled studies. Current evidence for use of the ketogenic diet is all based on class 1V studies: it is clear that more appropriate studies designs are needed to further evaluate its efficacy.

There is also a need to compare use of the two types of ketogenic diet. The only previous study to examine this question, in 55 children and 4 adults using either a classical, MCT, or modified MCT ketogenic diet, reported no statistically significant difference in short term clinical effects (Schwartz et al, 1989a): 22 of the 24 (92%) individuals using the classical diet had a greater than 50% seizure reduction, and 29 of the 39 (74%) individuals using either the MCT or modified MCT diet had a greater than 50% seizure reduction. However this study was non-randomized, and results were obtained after only 3 weeks; there are no other data comparing the two diets on either a short or longer-term basis.

A frequently asked question is whether certain types of seizure or syndrome will respond better to ketogenic diet treatment? It was traditionally thought to be most successful in treating patients with myoclonic or atonic seizures, or the mixed seizures seen in Lennox-Gastaut syndrome, however Freeman et al (1998) found no significant difference in efficacy between different types of seizure, including those of a focal

nature. Maydell (2001) also reported benefit in children with focal seizures; although there was a tendency for improved outcome in the generalized rather than focal seizure group, differences were not significant. In a study comparing children who showed a dramatic early response to diet treatment with a control group of unsuccessful children, Than et al (2005) found the absence of complex partial seizures in the early responders to be the only significant difference. Kang et al (2005) reported seizure outcomes for children with infantile spasms, Lennox-Gastaut syndrome, and nonspecific partial seizures (n=54) to be similar to each other, with no difference in outcome between the different seizure types presenting as part of the Lennox-Gastaut syndrome. To make a statistical comparison, the authors defined two outcome groups, favourable (>50% seizure reduction and continued diet beyond 12 months) and unfavourable (<50% seizure reduction and stopped diet before 12 months); there was no difference between children defined as having a symptomatic or cryptogenic etiology to their epilepsy, or between those whose pre-dominant seizure type was generalised or partial, although the partial seizure group and those with a symptomatic etiology were more likely to relapse after completing their treatment with the diet. Other seizure syndromes where good efficacy has been documented include infantile spasms (Kossoff et al, 2002b), severe myoclonic epilepsy of infancy (Caraballo et al, 2005), tuberous sclerosis complex (Kossoff et al, 2005), and myclonic astatic epilepsy (Oguni et al, 2002; Kilaru & Bergqvist, 2007),

The aim of this study was to conduct the first randomized controlled trial on the ketogenic diet, addressing two main questions:

1. Are there clear benefits in terms of seizure control in the group of children with epilepsy treated with a ketogenic diet as compared to a control group (no additional treatment)?
2. Is the classical ketogenic diet more efficacious than the MCT ketogenic diet in controlling seizures, as often claimed but not supported by scientific evidence.

3.2 Methods

3.2.1 Assessment of primary outcome – diet efficacy

The primary outcome of the study was a change in seizure activity. This was assessed by the following methods.

a) Parental/carer recording of seizures using specially designed charts (See appendix to chapter 3). Epilepsy syndrome was diagnosed where possible according to the latest diagnostic scheme proposed by the ILAE (Engel, 2001). Seizures were classified into 6 categories for recording (absence, myoclonic, atonic, tonic, tonic-clonic and focal). At the initial hospital consultation, a description of the child's seizures was discussed with a consultant paediatric neurologist, who then advised as to how they should be categorized for subsequent recording. Seizures were recorded daily for the 4 week baseline period, during the additional 3 months prior to starting the diet for the group acting as controls, and throughout the time a child was on the diet. The 28 days prior to a time point were used to calculate total seizure numbers at that time point, and mean daily seizure numbers were then calculated. These were expressed as a percentage of the mean daily seizure numbers during the 4-weeks prior to a child starting the diet (this was the 4 week baseline period for non-controls, and the last 4 weeks of the control period for the control group). Defined time points for assessment and analysis were 3 months, 6

months and 12 months on the diet. An additional time point at the end of the 3-month control period was used in the group acting as controls; mean daily seizure numbers over the last 4 weeks of this period were compared with those in the 4 week baseline period.

b) Anti-epileptic medication use was documented prior to starting the diet. After the initial 3 months of dietary treatment, during which medication was not changed, the aim was to progressively reduce medication dosages in children who were doing well in terms of seizure reduction.

A secondary outcome was to examine ketosis. Parents were asked to document urinary ketones twice daily. Blood samples were taken where possible from all children following a ketogenic diet at their outpatient clinic visits (before starting the diet and after 3, 6 and 12 months). Serum β-hydroxybutyrate and acetoacetate levels were measured in the hospital laboratories.

3.2.2 Sample size calculation

This trial was designed as comparative; the hypothesis being tested was that the classical diet might be more efficacious than the MCT diet as a treatment. Using a null hypothesis that the two diets were not significantly different in their effect on seizure control, and defining 25% as the minimum outcome difference of clinical importance, the sample size formula for comparing two means gave a necessary sample of 47 per diet group, allowing detection of a difference significant at 5% with a power of 90%. This was based on an expected outcome range of mean percentage of baseline seizures from 0 – 150% (standard deviation of 37.5%). This sample would allow detection of a 25% or more difference in mean percentage of baseline seizures

in the MCT diet group as compared to the classical diet group; any difference greater than this would be regarded as clinically significant.

3.2.3 Statistical analysis

Analysis for this thesis was based on total numbers of daily seizures; the more detailed subdivision into the six individual types, with subsequent changes in pattern of seizure activity, is not included. Statistical analyses were performed on the efficacy data as outlined below, in order to answer the following questions:

1. *Was there a significant difference in efficacy between diet and control groups?*

The unpaired t test was used to compare mean percentage of baseline seizure numbers after 3 months between children on a ketogenic diet and those acting as controls. For this analysis, only the diet data from the children who were not controls was used, to avoid any bias in the diet data provided by the control children resulting from the additional delay in commencing treatment. Multiple linear regression was used to examine the association between whether a child was on the diet or a control, and their percentage of baseline seizures, taking into account sex and age group (three age groups were defined, as for the initial randomization (2-6 years, 7-11 years, 12-16 years). Cut off points of greater than 50% and 90% seizure reduction were applied, and the Fishers exact test used to examine differences between diet and control groups in relation to these cut off points.

2. *How did the classical and MCT ketogenic diets compare in terms of efficacy?*

The unpaired t test was used to compare mean percentage of baseline seizure numbers in the classical and MCT diet groups after 3, 6 and 12 months. Data was provided from all children, both those who had started the diet after only 4-week baseline, and

those who had an additional 3-month control period before starting. Multiple linear regression was used to examine the association between which ketogenic diet a child was following, and their percentage of baseline seizure numbers, taking into account sex and age group. Cut off points of greater than 50% and 90% seizure reduction were applied, and the Fishers exact test used to examine differences between the two diet groups in relation to these cut off points. In children who continued the diet for 12 months, linear regression was used in each child separately to determine the gradient of the line of best fit of their serial values of percent baseline seizure numbers (3, 6 and 12 months). The resulting gradient value was used to represent the overall change in seizure numbers in that child over the 12-month period. The unpaired t-test was used to compare the mean gradient of the line of best fit between the two diet groups. The number of children who had their medication dosage reduced after 3 months treatment was also compared between the two diet groups using the Fishers exact test.

3. *Was there any difference in efficacy according to epilepsy syndromes?*

A number of syndrome groups were defined, and children allocated to one of these groups. The mean percentage of baseline seizure numbers was calculated for each syndrome group separately. Where possible, children were also categorized into two broad classifications of symptomatic generalized or symptomatic focal epilepsy, to allow a comparison of mean percentage of baseline seizure numbers between these two groups, using the unpaired t-test. In children who completed 12 months of treatment, this test was also used to compare the mean gradient of the line of best fit between symptomatic generalized and symptomatic focal groups.

4. *Was there any difference in ketosis between the two diet groups, and did this correlate with dietary efficacy?*

The unpaired t test was used to compare mean β-hydroxybutyrate and acetoacetate levels in the classical and MCT diet groups at baseline, and after 3, 6 and 12 months. Spearman's correlation coefficient was used to examine the association between a child's β-hydroxybutyrate and acetoacetate levels at each time point (3, 6 and 12 months), and their percentage of baseline seizures at that time.

SPSS software version 13 was used for all statistical analysis.

3.3 Results

3.3.1 Trial overview

Recruitment for the study commenced December 2001, and closed July 2006. This thesis is based on results collected by the end of 2007. Figures 3.1 and 3.2 illustrate the flow of children through each stage of the study.

Figure 3.1 Flow of children through the trial – diet V control

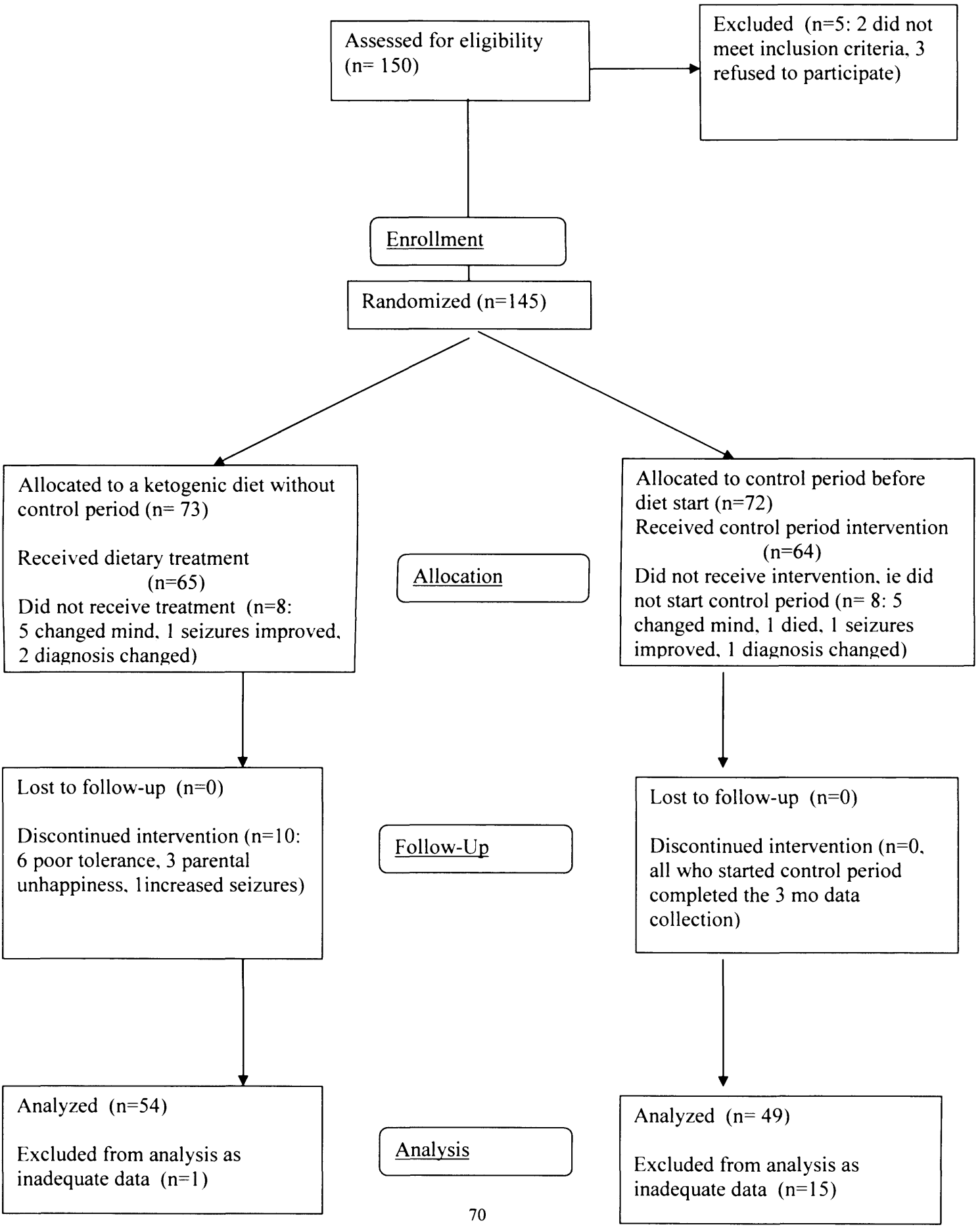
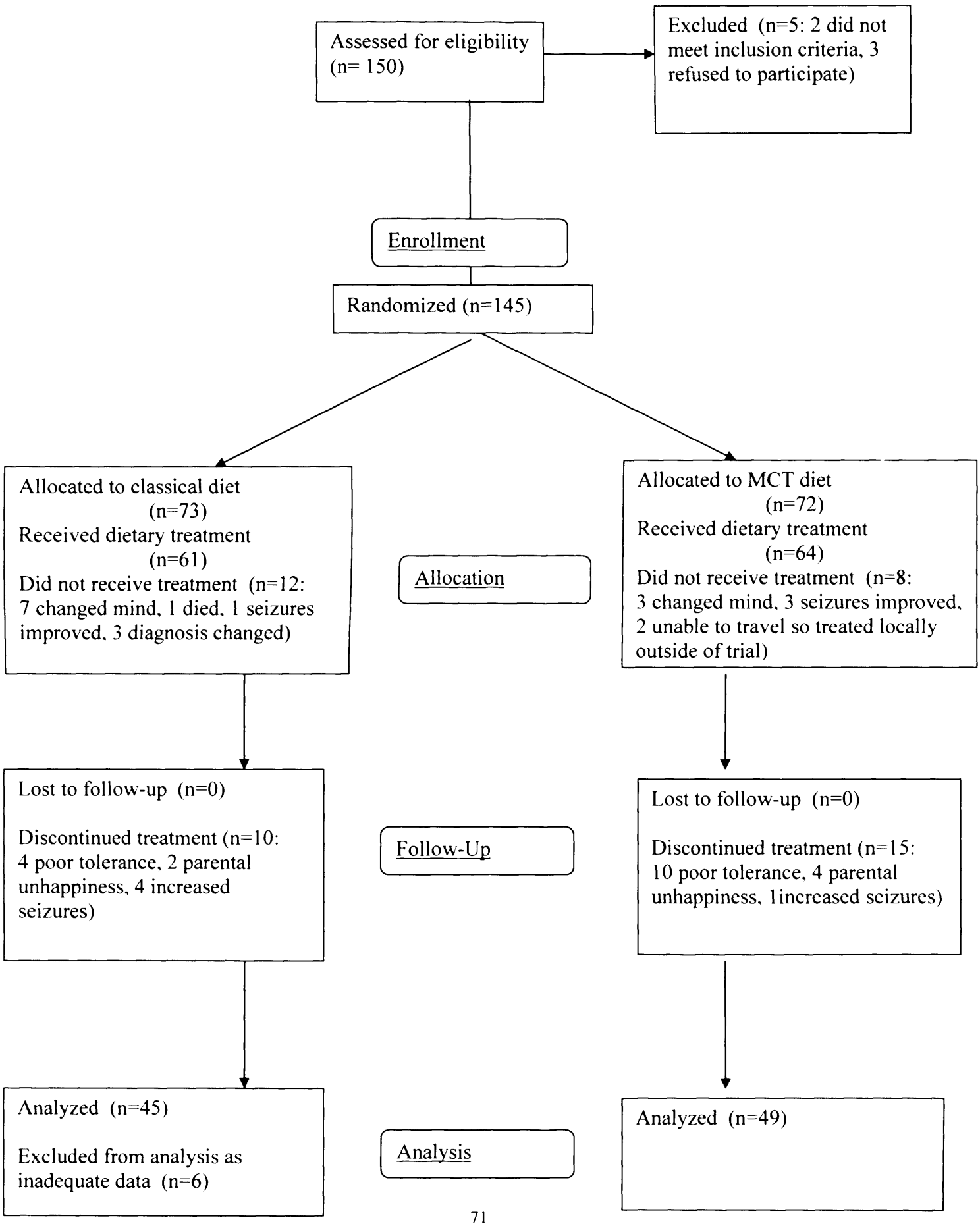


Figure 3.2 Flow of children through the trial – classical V MCT diet



The analysis was limited to those children from whom seizure data was available at the given time points. An 'intention to treat' analysis was not possible, as seizure data was not available on the other children not remaining on the diet. Baseline demographic characteristics of children randomized to, and included in the final analysis, of each of the study groups are given in tables 3.2 and 3.3.

Table 3.2 Baseline characteristics of children allocated to each study group and included in final analysis - diet V control

	Diet group		Control group	
	Allocated to study group (n=73)	Included in final analysis (n=54)	Allocated to study group (n=72)	Included in final analysis (n=49)
Boys	38 (52.1%)	30 (55.6%)	38 (52.8%)	25 (51.0%)
Girls	35 (47.9%)	24 (44.4%)	34 (47.2%)	24 (49.0%)
Aged 2-6 yrs	37 (50.7%)	28 (51.9%)	29 (40.3%)	20 (40.8%)
Aged 7-11 yrs	27 (37.0%)	20 (37.0%)	32 (44.4%)	20 (40.8%)
Aged 12-16 yrs	9 (12.3%)	6 (11.1%)	11 (15.3%)	9 (18.4%)

Table 3.3 Baseline characteristics of children allocated to each study group and included in final analysis – classical V MCT diet

	Classical diet group		MCT diet group	
	Allocated to study group (n=73)	Included in final analysis (n=45)	Allocated to study group (n=72)	Included in final analysis (n=49)
Boys	40 (54.8%)	26 (57.8%)	36 (50.0%)	25 (51.0%)
Girls	33 (45.2%)	19 (42.2%)	36 (50.0%)	24 (49.0%)
Aged 2-6 yrs	32 (43.8%)	21 (46.7%)	34 (47.2%)	24 (49.0%)
Aged 7-11 yrs	31 (42.5%)	16 (35.5%)	28 (38.9%)	20 (40.8%)
Aged 12-16 yrs	10 (13.7%)	8 (17.8%)	10 (13.9%)	5 (10.2%)

At the time of study entry, 6 children were on no epilepsy medications, 20 children were on one medication, 53 children on two medications, 54 children on three medications, 11 children on four medications, and one child on five medications. Children had a mean of 11.6 seizures daily (10.1 in control group v 13.3 in diet group; 9.9 in classical diet group v 13.3 in MCT diet group). Eight children were recruited from the residential centre; all others attended the hospital as outpatients while living at home. Of the residential centre group: one never started the diet due to parental circumstances, three stopped before 3 months (one intolerance, one parental unhappiness and one increased seizures), and two stopped at 3 months due to limited efficacy. Only two continued beyond 3 months of treatment.

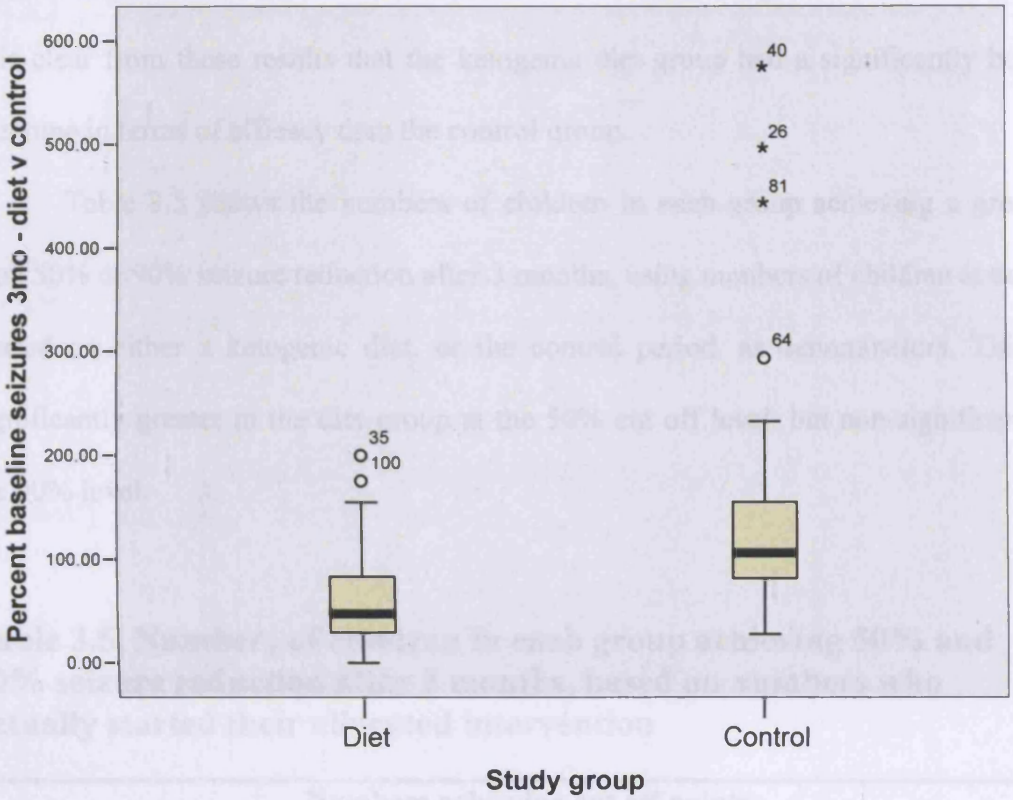
3.3.2. Comparison between diet and control groups

Table 3.4 shows results for percentage of baseline seizure numbers after 3 months in the diet and control groups. This is illustrated in Figure 3.3.

Table 3.4 Percentage of baseline seizure numbers after 3 months in diet and control groups

	Percent baseline seizures (%)	
	Diet group (n=54)	**Control group (n=49)**
Mean	62.01	136.93
95% confidence interval for mean	49.63 – 74.38	105.17 – 168.68
Median	47.65	106.25
Standard deviation	43.34	110.56
Range	0.00 – 200.00	28.21 – 575.00

Figure 3.3 Percentage of baseline seizure numbers in diet and control groups



The difference between the mean percentage baseline seizures in diet and control groups was 74.92% (95% confidence interval of difference 42.43 – 107.40). This difference was highly significant (p=0.000). Although data distribution is clearly skewed, with a number of outliers, and a digression between mean and median values for both groups, this difference remained at the same highly significant level when additionally tested using non-parametric methods (Mann-Whitney *U*). Removal of outliers before analysis lowered the mean difference to 44.05% (95% confidence interval of difference 25.46 – 62.64), but this remained highly significant (p=0.000). Using a linear regression model to take into account the sex and age group of the child, the difference between the mean percentage baseline seizures in diet and control groups increased slightly to 76.63% (95% confidence interval of difference 44.37 –

108.89): this was still highly significant (p=0.000). Although the wide confidence intervals represent the data to be compatible with a broad range of clinical scenarios, it is clear from these results that the ketogenic diet group had a significantly better outcome in terms of efficacy than the control group.

Table 3.5 shows the numbers of children in each group achieving a greater than 50% or 90% seizure reduction after 3 months, using numbers of children actually started on either a ketogenic diet, or the control period, as denominators. This is significantly greater in the diet group at the 50% cut off level, but non-significant at the 90% level.

Table 3.5. Numbers of children in each group achieving 50% and 90% seizure reduction after 3 months, based on numbers who actually started their allocated intervention

	Numbers achieving cut off points		p value
	Diet group (n=65)	Control group (n=64)	
Greater than 90% seizure reduction	5 (7.7%)	0	0.0577
Greater than 50% seizure reduction	28 (43.1%)	4 (6.3%)	≤0.0001

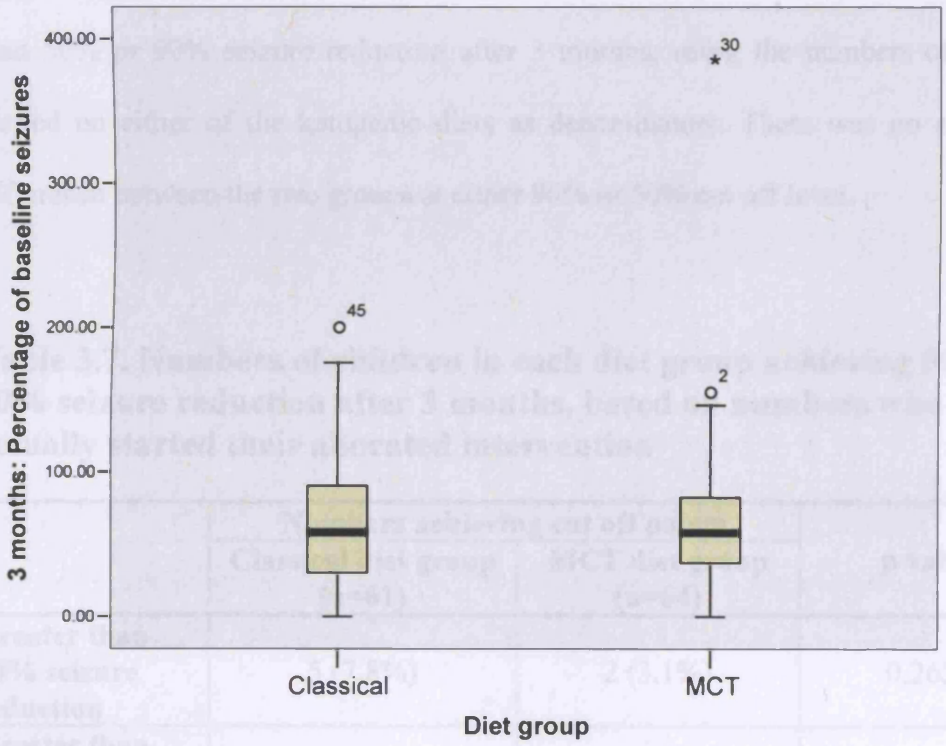
3.3.3. Comparison between classical and MCT diet groups after 3 months

Table 3.6 shows results for percentage of baseline seizure numbers after 3 months in the two diet groups. This is illustrated in Figure 3.4.

Table 3.6 Percentage of baseline seizure numbers after 3 months in classical and MCT diet groups

	Percent baseline seizures (%)	
	Classical diet group (n=45)	MCT diet group (n=49)
Mean	66.50	68.85
95% confidence interval for mean	52.29 – 80.73	51.77 – 85.93
Median	58.14	58.12
Standard deviation	47.34	59.47
Range	0.00 – 200.00	0.00 - 385.71

Figure 3.4 Percentage of baseline seizure numbers after 3 months in classical and MCT diet groups



The mean percentage of baseline seizure numbers after 3 months was 2.45% lower in the classical diet group (95% confidence interval of difference -19.80 – 24.29). This difference was not significant (p=0.834). Figure 3.4 shows the data had one extreme outlier in the MCT diet group, on reanalysis excluding this outlier; the mean

percentage of baseline seizures in the MCT diet group fell to 62.25% (standard deviation 37.83%). This was 4.26% lower than the classical diet group (95% confidence interval of difference 13.34 – 21.85), and still non-significant (p=0.632). Using a linear regression model to take into account the sex and age group of the child, the difference between the mean percentage baseline seizures in the two diet groups increased very slightly to 3.45% (95% confidence interval of difference -19.22 – 26.11), still non-significant (p=0.763). These results show that after 3 months of ketogenic diet treatment, there was no difference in terms of efficacy between the classical or MCT diet protocols.

Table 3.7 shows the numbers of children in each diet group achieving a greater than 50% or 90% seizure reduction after 3 months, using the numbers of children started on either of the ketogenic diets as denominators. There was no significant difference between the two groups at either 90% or 50% cut off level.

Table 3.7. Numbers of children in each diet group achieving 50% and 90% seizure reduction after 3 months, based on numbers who actually started their allocated intervention

	Numbers achieving cut off points		p value
	Classical diet group (n=61)	MCT diet group (n=64)	
Greater than 90% seizure reduction	5 (7.8%)	2 (3.1%)	0.2656
Greater than 50% seizure reduction	18 (29.5%)	21 (32.8%)	0.7043

After 3 months of treatment, 26 children on the classical diet and 27 children on the MCT diet were able to have their anti-epileptic medication dose reduced (p= 0.841).

3.3.4. Comparison between classical and MCT diet groups after 6 and 12 months

Fewer numbers of children provided seizure data at 6 and 12 months, due in part to children discontinuing diet treatment, and in part to unavailable data for analysis. Table 3.8 gives numbers of children providing data for analysis at each time point and reasons why some data was unavailable.

Table 3.8. Flow of children through the study after 3 months

	Numbers of children	
	Classical diet	**MCT diet**
Discontinued diet after 3 month follow up	9	11
Moved away after 3 month follow up	1	0
Data available for 6 month analysis	30	34
Discontinued diet after 6 month follow up	5	5
Discontinued diet after 9 months treatment	1	1
Data available for 12 month analysis	22	25
Data unavailable at 6 and 12 months	5	4

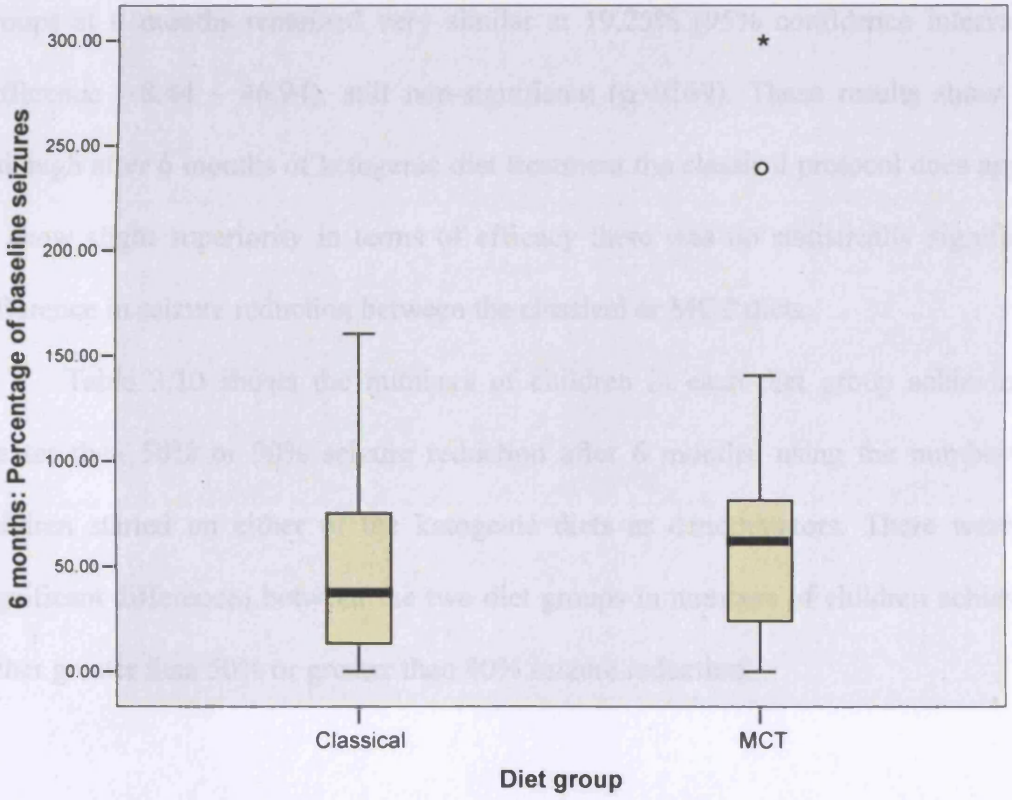
Of the 45 children on the classical diet who had seizure data analysed at 3 months, 9 discontinued treatment after the 3 month follow up visit (20%); of the 49 children on the MCT diet who had seizure data analysed at 3 months, 11 discontinued treatment after the 3 month follow up visit (22.4%). Reasons for discontinuation at this point were based on limited efficacy, the psychosocial costs of following the strict dietary regime outweighing the benefit seen in terms of seizure reduction. A further 10 children (5 on each diet) discontinued for the same reason after the 6 month follow up, and 2 more after 9 months. By 12 months, 32 children out of the original 94 who provided 3-month data (34%) had stopped treatment. Data was unavailable for 9 children who had completed 12 months of treatment, but failed to keep adequate records.

Table 3.9 shows results for percentage of baseline seizure numbers after 6 months in the two diet groups. This is illustrated in Figure 3.5.

Table 3.9 Percentage of baseline seizure numbers after 6 months in classical and MCT diet groups

	Percent baseline seizures (%)	
	Classical diet group (n=30)	MCT diet group (n=34)
Mean	48.53	67.62
95% confidence interval for mean	32.40 – 64.67	45.86 – 89.39
Median	37.51	62.05
Standard deviation	43.21	62.36
Range	0 – 160.53	0 – 300.00

Figure 3.5 Percentage of baseline seizure numbers after 6 months in classical and MCT diet groups



The mean percentage of baseline seizure numbers after 6 months was 19.09% lower in the classical diet group (95% confidence interval of difference –8.08 - 46.25). This difference was non-significant (p=0.165). Data distribution appears skewed, with some digression between mean and median values, especially in the classical diet group, however a similar significance level was seen when an additional non-parametric test was applied (Mann-Whitney *U*, p=0.213). There were two extreme outliers in the MCT diet group, on reanalysis excluding these outliers; the mean percentage of baseline seizures in the MCT diet group fell to 55.01% (standard deviation 35.87%). This was 6.47% higher than the classical diet group (95% confidence interval of difference 13.65 - 26.60), (p=0.522).

Using a linear regression model to take into account the sex and age group of the child, the difference between the mean percentage baseline seizures in the two diet groups at 6 months remained very similar at 19.25% (95% confidence interval of difference -8.44 – 46.94), still non-significant (p=0169). These results show that although after 6 months of ketogenic diet treatment the classical protocol does appear to show slight superiority in terms of efficacy there was no statistically significant difference in seizure reduction between the classical or MCT diets.

Table 3.10 shows the numbers of children in each diet group achieving a greater than 50% or 90% seizure reduction after 6 months, using the numbers of children started on either of the ketogenic diets as denominators. There were no significant differences between the two diet groups in numbers of children achieving either greater than 50% or greater than 90% seizure reduction.

Table 3.10. Numbers of children in each diet group achieving 50% and 90% seizure reduction after 6 months, based on numbers of children who actually started their allocated intervention

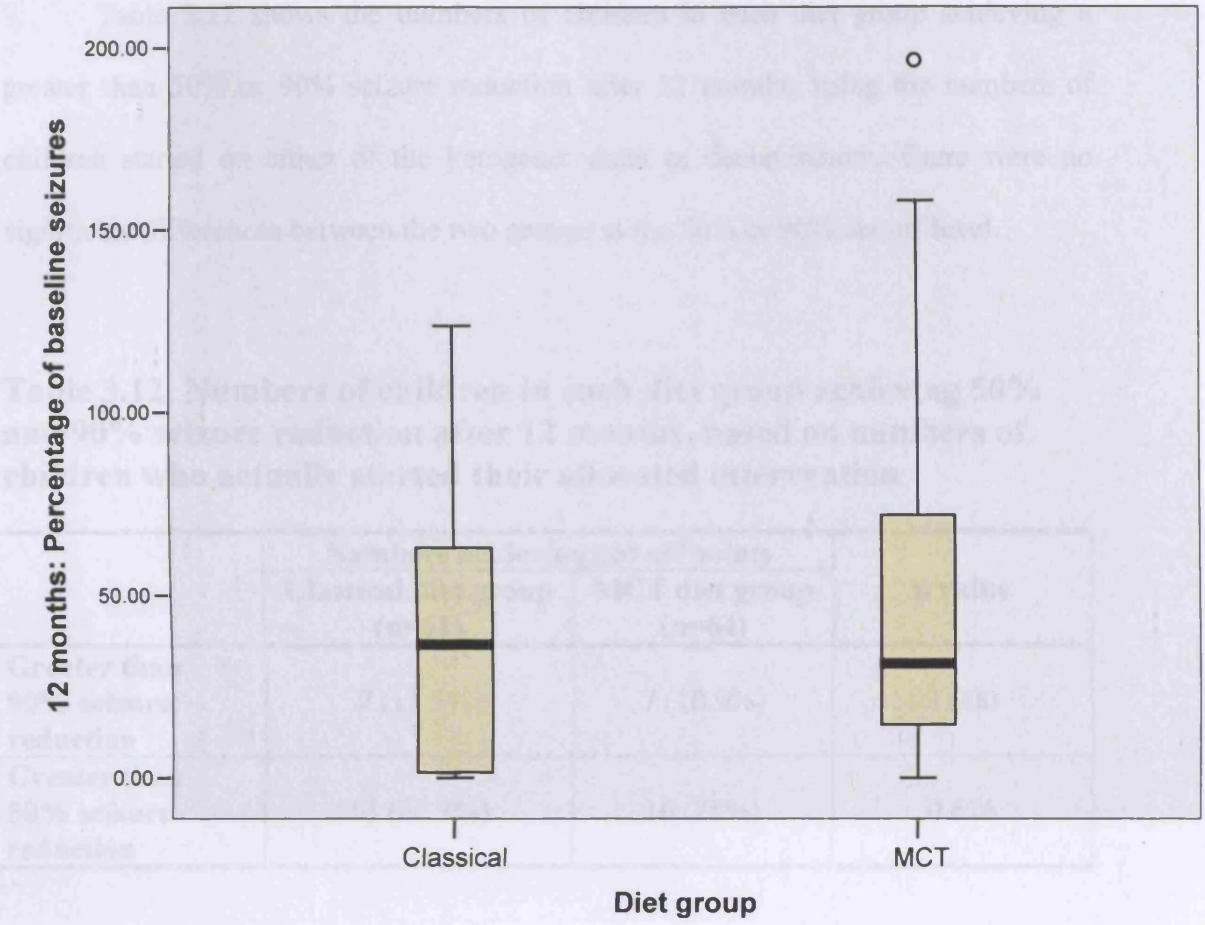
	Numbers achieving cut off points		p value
	Classical diet group (n=61)	MCT diet group (n=64)	
Greater than 90% seizure reduction	6 (9.8%)	4 (6.3%)	0.524
Greater than 50% seizure reduction	18 (29.5%)	14 (21.9%)	0.413

Table 3.11 shows results for percentage of baseline seizure numbers after 12 months in the two diet groups. This is illustrated in Figure 3.6.

Table 3.11 Percentage of baseline seizure numbers after 12 months in classical and MCT diet groups

	Percent baseline seizures (%)	
	Classical diet group (n=22)	MCT diet group (n=25)
Mean	40.83	53.16
95% confidence interval for mean	24.08 – 57.57	30.42 – 75.91
Median	36.55	31.29
Standard deviation	37.77	55.10
Range	0 – 123.72	0 – 196.52

Figure 3.6 Percentage of baseline seizure numbers after 12 months in classical and MCT diet groups



The mean percentage of baseline seizure numbers after 12 months was 12.34% lower in the classical diet group (95% confidence interval of difference –15.81 – 40.47). This difference was non-significant (p=0.382). Although this mean percentage was lower in the classical diet group, the median was lower in the MCT group. Using a linear regression model to take into account the sex and age group of the child, the difference between the mean percentage baseline seizures in the two diet groups at 12 months remained similar at 12.53% (95% confidence interval of difference –16.09 – 41.14), non-significant (p=0.382). These results show that although after 12 months of

ketogenic diet treatment there were no significant differences between the two protocols.

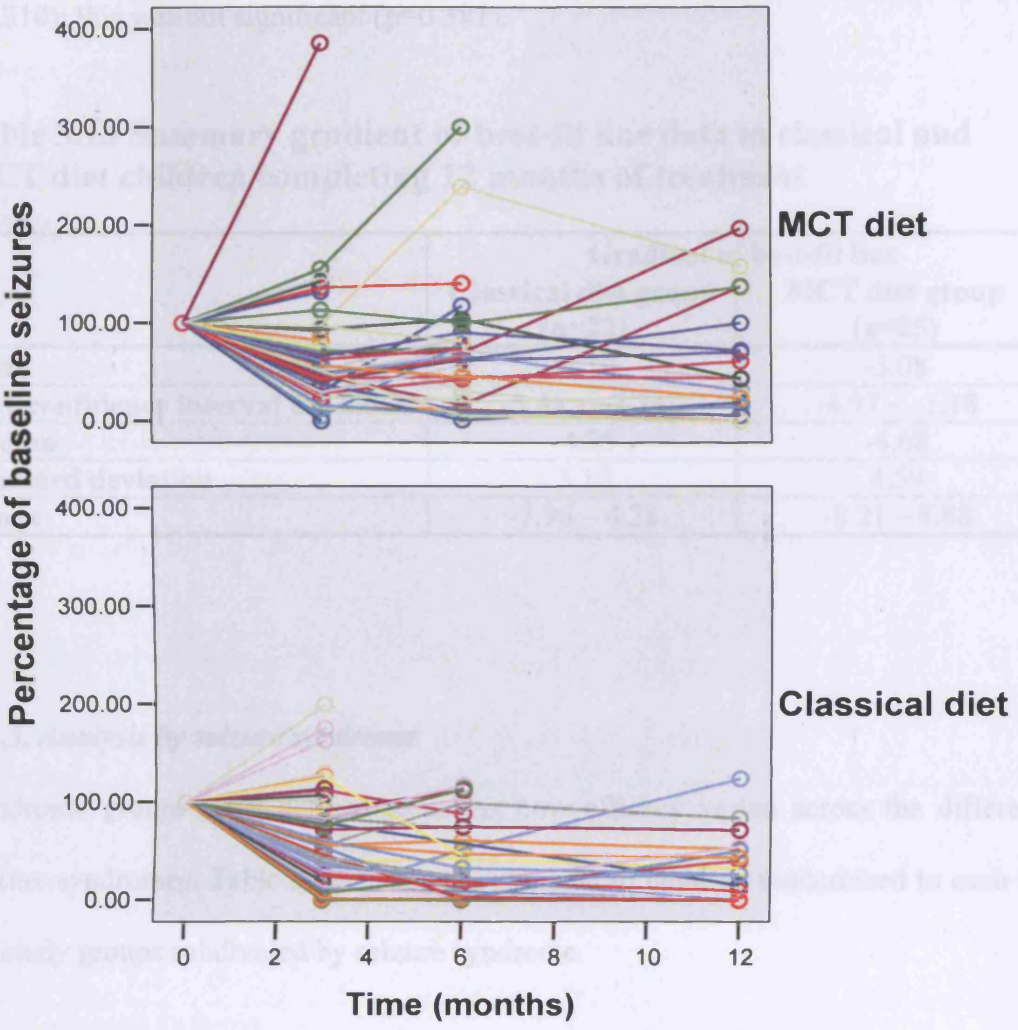
Table 3.12 shows the numbers of children in each diet group achieving a greater than 50% or 90% seizure reduction after 12 months, using the numbers of children started on either of the ketogenic diets as denominators. There were no significant differences between the two groups at the 50% or 90% cut off level.

Table 3.12. Numbers of children in each diet group achieving 50% and 90% seizure reduction after 12 months, based on numbers of children who actually started their allocated intervention

	Numbers achieving cut off points		p value
	Classical diet group (n=61)	MCT diet group (n=64)	
Greater than 90% seizure reduction	7 (11.5%)	7 (10.9%)	1.000
Greater than 50% seizure reduction	13 (21.3%)	16 (25%)	0.676

The overall change in percentage of baseline seizure numbers for individual children, during the course of the 12-month study period, was plotted for the two diets separately (Figure 3.7).

Figure 3.7. Overall change in percentage baseline seizure numbers over 12 months in children on the classical and MCT ketogenic diets



Although these graphs allow visualisation of overall trends, it is difficult to see any clear patterns without more detailed statistical analyses. In children who completed 12 months of dietary treatment, the use of a gradient of the line of best-fit technique allowed a value to be assigned to each individual; this value representing their overall pattern of change in seizure frequency during the 12 months. Summary gradient data for each diet group was then analysed (Table 3.13). Although there is considerable variation between individuals in their pattern of change in seizure frequency, both diet

groups as a whole appear similar: the mean difference in gradient between the classical and MCT groups was –1.025 (95% confidence interval of difference –3.360 – 1.310); this was not significant (p=0.381).

Table 3.13 Summary gradient of best-fit line data in classical and MCT diet children completing 12 months of treatment

	Gradient of best-fit line	
	Classical diet group (n=22)	**MCT diet group (n=25)**
Mean	-4.10	-3.08
95% confidence interval for mean	-5.48 - -2.73	-4.97 - -1.18
Median	-4.35	-4.68
Standard deviation	3.10	4.59
Range	-7.96 – 4.28	-8.21 – 8.88

3.3.5. Analysis by seizure syndrome

Syndrome groups were defined to assess how efficacy varied across the different seizure syndromes. Table 3.14 shows the numbers of children randomized to each of the study groups subdivided by seizure syndrome.

Table 3.14. Numbers of children allocated to study groups, by syndrome

Syndrome diagnosis	Numbers allocated to each study group			
	Diet v control		Classical v MCT	
	Diet group (n=73)	Control group (n=72)	Classical group (n=73)	MCT group (n=72)
Symptomatic generalised (unspecified)	11	11	8	14
Symptomatic focal:				
- focal (no brain abnormality specified)	9	7	9	7
- multifocal (no brain abnormality specified)	5	9	8	6
- structural brain malformation (including tuberous sclerosis)	15	12	13	14
SMEI (severe myoclonic epilepsy of infancy)	2	5	3	4
Lennox-Gastaut syndrome	7	7	6	8
West syndrome (Infantile spasms)	6	5	8	3
Myoclonic absence epilepsy	4	3	4	3
Myoclonic epilepsy (unspecified)	2	6	5	3
Myoclonic astatic epilepsy	4	4	1	7
Atypical absence epilepsy	1	2	2	1
Childhood absence epilepsy	2	0	0	2
Degenerative conditions	3	0	3	0
Early myoclonic encephalopathy	0	1	1	0
ESESS (electrical status epilepticus of slow sleep)	2	0	2	0

Due to the small numbers in the last five groups, these were excluded from the syndrome analysis. Table 3.15 shows the mean percentage of baseline seizures after 3,

6 and 12 months in each of the remaining syndrome groups, based on the numbers of children from whom data was available for analysis at each of the time points.

Table 3.15. Mean percentage of baseline seizures at 3, 6 and 12 months in defined syndrome groups

	Mean (SD) percentage baseline seizure numbers at each time point (number of children in each group providing data at that time point)		
	3 months	**6 months**	**12 months**
Symptomatic generalised (unspecified)	73.23% (53.87) (n=11)	68.10% (36.82) (n=7)	73.46% (89.84) (n=2)
Symptomatic focal:			
- focal (no brain abnormality specified)	74.70% (40.42) (n=12)	63.20% (40.51) (n=8)	23.85% (17.76) (n=4)
- multifocal (no brain abnormality specified)	92.15%(109.05) (n=11)	86.08% (129.25) (n=5)	50.42% (n=1)
-structural brain malformation (including tuberous sclerosis)	67.34% (33.55) (n=18)	47.49% (41.96) (n=9)	25.15% (29.07) (n=7)
SMEI	77.61% (32.0) (n=5)	64.15% (51.91) (n=3)	0% (n=1)
Lennox-Gastaut syndrome	50.50% (34.89) (n=11)	40.57% (29.52) (n=10)	60.67% (64.84) (n=9)
West syndrome	72.82% (68.09) (n=6)	44.98% (26.67) (n=4)	58.49% (51.10) (n=4)
Myoclonic absence epilepsy	54.94% (19.39) (n=4)	87.84% (12.33) (n=3)	77.60% (7.91) (n=2)
Myoclonic epilepsy (unspecified)	58.68% (23.72) (n=8)	71.93% (85.20) (n=6)	66.56% (53.11) (n=6)
Myoclonic astatic epilepsy	58.21% (65.98) (n=4)	3.5% (4.95) (n=2)	7.31% (10.33) (n=2)

The numbers in each group providing data at 3, 6 and 12 months were too small for between-group statistical analysis: a between-group comparison of the mean gradients of the best fit lines in children completing 12 months was also not possible due to small numbers.

Two additional categories were defined: all seizure syndrome groups that could be grouped together as being symptomatic generalised in origin, and all seizure syndrome groups that could be grouped together as being symptomatic focal in origin. Of the 125 children who started dietary treatment, 114 were able to have their seizures broadly classified in this way (62 symptomatic generalised, 52 symptomatic focal); not all seizure syndromes could be included. Table 3.16 shows the mean percentage of baseline seizures after 3, 6 and 12 months in these two groups: there were no significant differences at 3 and 6 months, the difference at 12 months was just significant.

Table 3.16. Mean percentage of baseline seizures at 3, 6 and 12 months in symptomatic generalised and symptomatic focal groups

Time point	Mean (SD) percentage baseline seizure numbers at each time point (number of children in each group providing data at that time point)		
	Symptomatic generalised	Symptomatic focal	p value
3 months	59.62% (44.31) (n=44)	76.15% (63.29) (n=41)	0.164
6 months	58.40% (45.82) (n=32)	61.97% (68.03) (n=22)	0.819
12 months	61.73% (54.57) (n=24)	26.82% (24.55) (n=12)	0.043

In the children who completed 12 months of treatment, the mean gradients of the line of best fit of their serial percentage of baseline seizure values were compared. This was significantly lower in the symptomatic focal group (-5.51) than in the

symptomatic generalised groups (-2.16; p=0.022); the focal group therefore showing a more significant trend in seizure reduction over the 12 months.

3.3.6. Ketosis and seizure control

Table 3.17 and Figure 3.8 show the serum β-hydroxybutyrate levels in the children on the classical and MCT ketogenic diets at each time point. The mean level was higher in the classical diet group after 3, 6 and 12 months of treatment; this was significant at 3 and 6 months only. However, there was a wide range in individual values, with the highest level at all time points on the diet seen in a child on the MCT diet.

Table 3.17. Serum β-hydroxybutyrate levels in children on classical and MCT ketogenic diets

Time (months)	β-hydroxybutyrate level (mmol/l) Mean ± SD (range), (no of children from whom data available)		p value
	Classical diet	MCT diet	
0	0.08 ± 0.13 (<0.05 – 0.86) (n=42)	0.07 ± 0.67 (<0.05 – 0.46) (n=49)	0.596
3	4.21 ± 1.73 (0.11 – 7.32) (n=42)	2.71 ± 1.70 (0.05 – 8.22) (n=45)	0.000
6	4.21 ± 1.44 (1.10 – 6.84) (n=32)	2.76 ± 1.81 (0.15 – 6.87) (n=37)	0.001
12	4.24 ± 1.69 (1.05 – 8.28) (n=22)	3.37 ± 2.81 (0.05 – 9.65) (n=22)	0.224

Figure 3.8. Serum β-hydroxybutyrate levels in children on classical and MCT ketogenic diets

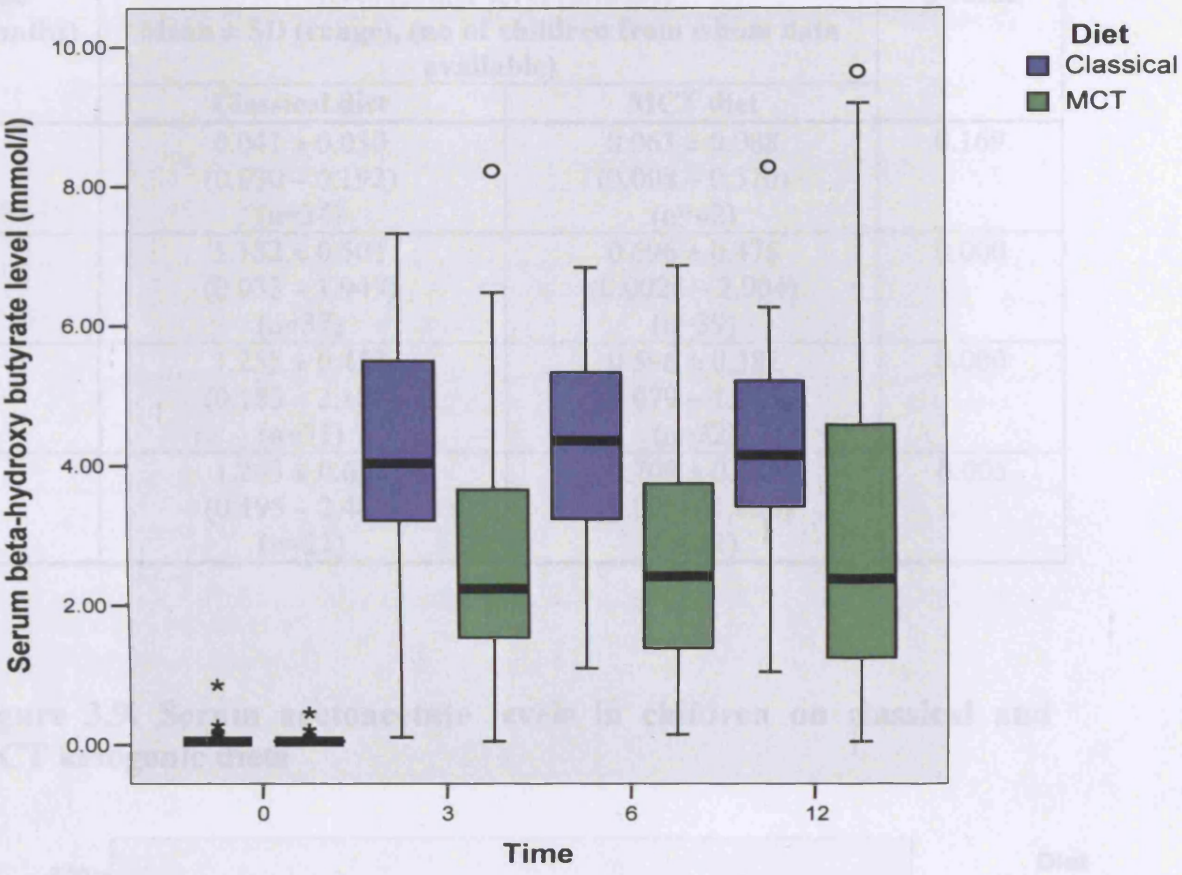
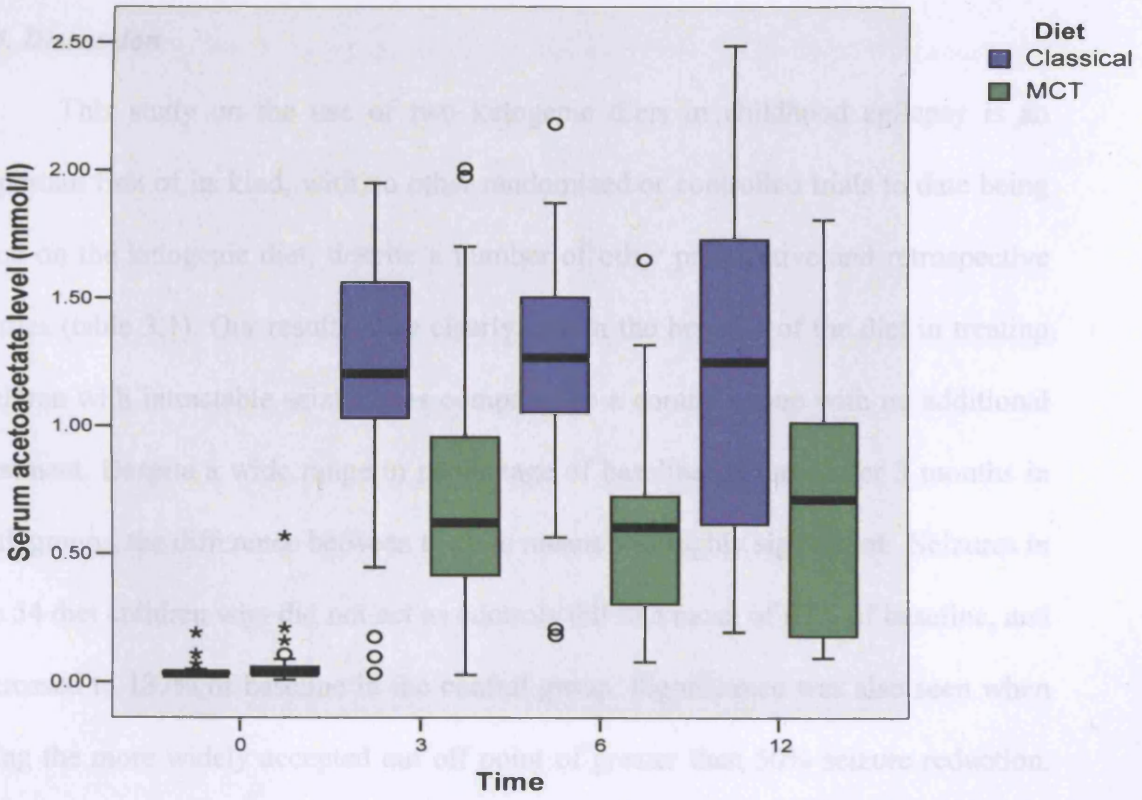


Table 3.18 and Figure 3.9 show the serum acetoacetate levels in the children on the classical and MCT ketogenic diets at each time point. The mean level was significantly higher in the classical diet group after 3, 6 and 12 months, although there was again a wide range in values during the course of the study.

Table 3.18. Serum acetoacetate levels in children on classical and MCT ketogenic diets

Time (months)	Acetoacetate level (mmol/l) Mean ± SD (range), (no of children from whom data available)		p value
	Classical diet	MCT diet	
0	0.041 ± 0.030 (0.030 – 0.192) (n=34)	0.063 ± 0.088 (0.008 – 0.570) (n=42)	0.169
3	1.182 ± 0.501 (0.033 – 1.949) (n=37)	0.696 ± 0.475 (0.0028 – 2.004) (n=39)	0.000
6	1.255 ± 0.453 (0.183 – 2.180) (n=31)	0.596 ± 0.382 (0.079 – 1.648) (n=32)	0.000
12	1.263 ± 0.692 (0.195 – 2.485) (n=21)	0.709 ± 0.485 (0.095 – 1.806) (n=21)	0.005

Figure 3.9. Serum acetoacetate levels in children on classical and MCT ketogenic diets



The correlation between ketone levels and seizure control was examined for all children on a ketogenic diet, using Spearman's correlation coefficient (Table 3.19). This was significant for both ketone bodies at 3 months, but not at 6 and 12 months.

Table 3.19. Correlation of serum ketone levels with percentage of baseline seizure frequency

Time (months)	Correlation with percentage of baseline seizure frequency			
	β-hydroxybutyrate		Acetoacetate	
	Correlation coefficient	p value	Correlation coefficient	p value
3	-0.238	0.036*	-0.312	0.009**
6	-0.058	0.673	-0.204	0.147
12	0.158	0.366	0.187	0.297

*** significant at p<0.05 level**
**** significant at p<0.01 level**

3.4. Discussion

This study on the use of two ketogenic diets in childhood epilepsy is an important first of its kind, with no other randomized or controlled trials to date being done on the ketogenic diet, despite a number of other prospective and retrospective studies (table 3.1). Our results have clearly shown the benefits of the diet in treating children with intractable seizures, as compared to a control group with no additional treatment. Despite a wide range in percentage of baseline seizures after 3 months in both groups, the difference between the two means was highly significant. Seizures in the 54 diet children who did not act as controls fell to a mean of 62% of baseline, and increased to 137% of baseline in the control group. Significance was also seen when using the more widely accepted cut off point of greater than 50% seizure reduction.

The use of cut off points allows a comparison with other ketogenic diet studies employing the same levels. 43% of our 65 non-control diet children who actually started their allocated intervention had a greater than 50% seizure reduction after 3 months; 8% had a greater than 90% seizure reduction. When the group of 94 children who provided diet data for analysis was looked at as a whole, results were very similar (41% and 8% respectively).

Analysis by seizure syndrome after 3 months shows children with Lennox-Gastaut and the myoclonic epilepsies to have the best outcomes on the diet, although statistical comparisons were not possible due to the small numbers in each group. When children with seizures of symptomatic generalised origin were compared to those of symptomatic focal origin, the 3 and 6-month results show the former group to have a better outcome; this was reversed by 12 months. However, the numbers remaining on the diet in the focal group were smaller; 24 of the 62 symptomatic generalised children who started the diet (38%) were still on treatment at 12 months, compared to 12 of the 52 symptomatic focal children (23%). Of the five children who stopped the diet before 3 months due to increased seizures, two had epilepsy of a symptomatic generalised and three of a symptomatic focal origin.

On comparing our 3-month efficacy results with the literature, it can be seen that results in our children on the diet achieving greater than 50% reduction are similar to those reported by Coppola et al (2002), Kankirawatana et al (2001), and Maydell et al (1999) in their groups of 56, 35, and 143 children respectively, who had been on the classical diet for 3 months. The USA multicentre study (Vining et al, 1998) found 54% of children to have a greater than 50% seizure reduction after 3 months, and the two largest studies (Freeman et al, 1998; Kang et al, 2005) both

reported just under two thirds of those starting the diet to have greater than 50% seizure reduction after 3 months; all using the classical protocol.

The main difference between our results and other studies is that other groups report a much higher number of children, within the greater than 50% cut off group, who actually have a greater than 90% reduction. 19-56% of children are reported to have a greater than 90% seizure reduction after 3 months on the diet in previous studies (table 3.1); the two with the largest number of children (Freeman et al, 1998; Kang et al, 2005) reporting 33% and 43% respectively. Why could our results show this inferior difference? One possibility is at the study selection stage. The scarce nature of ketogenic diet services in the UK, and the lack of medical awareness about the treatment, have meant that it is often viewed as a last resort after everything else has failed. The children referred to our trial therefore had very severe intractable epilepsy, usually having explored many other treatment options over a number of years. Inclusion criteria required at least seven seizures weekly, and having tried at least two anticonvulsant medications. In fact, at the time of study entry, our children had a mean of 12 seizures daily. 53 children (37%) were on two medications, 54 children (37%) on three medications, 11 children (8%) on four medications, and one child on five medications. Minimum seizure numbers for entry into the two other larger studies were lower; at least two seizures weekly (Freeman et al, 1998), or four seizures monthly (Kang et al, 2005) Although both these studies required children to have tried at least two (Freeman et al, 1998), or three (Kang et al, 2005) anticonvulsant medications, the inclusion of children with considerably lower numbers of seizures at baseline could have resulted in improved outcomes; this may go some way in explaining the discrepancy in results from our study. In addition, our study did not include children less than two years of age; there is some evidence that

this age group may respond more favourably than older children (Kossoff et al 2002b, Nordli et al 2001).

Critics of the MCT diet protocol (Freeman et al, 2000) may argue that our results were negatively influenced by including children on both diets, that the superior outcomes seen in other studies were due to use of the classical protocol alone. However, the studies reported in Table 3.1 do include the use of both protocols, albeit the MCT in much smaller numbers. Our results do not show the classical diet to be significantly better in terms of efficacy outcome. At 3 months, a wide range in percentage of baseline seizures was seen in both classical and MCT groups, however the two means (67% and 69% respectively) were not significantly different; indeed after exclusion of one extreme outlier in the MCT group, this mean fell to 62%. There were also no significant differences between the groups in the numbers achieving greater than 50% and 90% seizure reduction, or reducing medication dose after 3 months.

Results after 6 and 12 months also do not show significant differences between the classical and MCT diet. 20 children discontinued the diet after their 3-month follow-up due to limited efficacy (9 classical and 11 MCT, in total 16% of those starting one of the two diets); a further 10 discontinuing after their 6-month follow-up (5 each diet, in total 8% of those starting one of the two diets). Nine additional children were unable to provide their 6 and 12-month data for analysis. Although 6-month results show the 30 children in the classical diet group to have a slightly better outcome, with a 19% lower mean percentage of baseline seizures, this was not statistically significant, and was reduced to only 6% by removal of the outlier. At 12 months, the classical diet again appeared to be slightly superior, with a 12% lower mean percentage of baseline seizures, but this was not statistically significant.

There were no significant differences between the groups in the numbers achieving greater than 50% and 90% seizure reduction at 6 or 12 months. The use of a gradient of line of best fit of serial measures in children who completed 12 months of dietary treatment is recommended as the appropriate statistical methodology for this type of data (Matthews et al, 1990); allowing a mean gradient to be obtained for the two diet groups, and thus a statistical comparison of overall change in seizures to be made between the groups. The mean gradient in the 22 classical diet children was more negative than in the 25 MCT children, indicating more of a reduction in percentage of baseline seizures over the 12 months, however this was not significant. Although a larger sample size would have been beneficial, these results do not support the hypothesis that the classical diet is significantly better in terms of seizure control. It is not possible from this study however to conclude equal effectiveness. This would require an equivalence study design as opposed to a comparative study design, which would require a much larger sample size (Jones et al, 1996), only achievable by using a multi-centre study design, run over many years.

In our study, mean levels of β-hydroxybutyrate and acetoactetate in the blood were significantly higher in the classical diet group, although all diets were fine-tuned with the aim of children achieving a high level of urinary ketones (8-16mmol per litre), and very high blood ketone levels were found in certain individuals on both diets. The increased ketosis in the classical diet group could be expected, as the MCT diet allows more carbohydrate, with a lower total fat level because of the highly ketogenic nature of the MCT. The increased dietary carbohydrate, especially if daily distribution is not carefully controlled, may adversely affect the state of high ketosis seen in ketogenic diet children. Schwartz et al (1989b) also found significantly higher blood ketone body levels in their classical diet group during 24-hour blood profiles

measured 3 weeks after starting the diet; no significant difference was seen between the MCT and modified MCT groups, despite the different level of MCT fat in these two protocols.

The relationship between seizure control and ketosis is still unclear. Whereas some authors suggest ketones must be at a sufficient level to achieve seizure control (Gilbert et al, 2000; Huttenlocher, 1976), the link between ketosis and seizure control has been questioned (Bough et al, 2000; Cunnane, 2004). A recent randomized study comparing the 3:1 and 4:1 classical diets in 76 children found the higher ratio diet to have significantly greater anti-epileptic efficacy, however there were no significant differences in the β-hydroxybutyrate levels between the two groups (Seo et al, 2007). Some animal models have shown ketone bodies to exert direct anticonvulsant action, but β-hydroxybutyrate is thought to be less important than acetoacetate (Likhodi & Burnham, 2004), and acetone suggested as the most important of the ketone bodies (Kalapos, 2007; Gasior et al, 2007). Our results did show some correlation between seizure control and ketosis, however this was only at 3 months. A clear linear relationship may not actually exist; other ketosis-induced metabolic changes may be more important in seizure control.

A number of hypotheses on mechanism of action have emerged over the past few years. One involves the effect of the diet on cerebral energy metabolism; with failure to meet brain energy needs contributing to the initiation and spread of epileptic activity (Nordli & DeVivo, 2004). The ketogenic diet will increase brain energy reserves by bypassing less efficient glycolysis pathways, and maximizing tricarboxylic acid cycle function. This may influence seizure activity by increased production of inhibitory neurotransmitters, improved ability to buffer the extra-cellular milieu, or alteration of resting membrane potential ((Nordli & DeVivo, 2004).

The reduction in glycolytic energy supply may activate ATP-sensitive potassium channels, which may regulate seizure threshold (Schwartzkroin, 1999; Bough & Rho, 2007). Fructose-1,6-bisphosphate, important in shifting glucose metabolism away from glycolysis, may also have a role (Lian et al, 2007).

An alternative hypothesis is the alteration of brain amino-acid handling. Utilization of ketone bodies as a brain substrate will alter metabolism of glutamate, an important excitatory neurotransmitter. Reduced transamination of glutamate to aspartate increases glutamate availability for synthesis of the main inhibitory brain neurotransmitter, gamma amino butyric acid (GABA), both directly, and via glutamine production (Yudkoff et al, 2004). A hypothesis by Cullingford (2004) is the involvement of metabolic adaptations to the diet, mediated at the molecular level by sensor mechanisms. The fatty-acid activated transcription factor peroxisome proliferator-activated receptor α (PPARα), activated by ketogenesis, may be important in the anti-epileptic effects of the diet, by influencing neurotransmitter metabolism. Other researchers have suggested the role of neuropeptides and norepinephrine. Anticonvulsant neuropeptides, galanin and neuropeptide Y, which are stimulated by nutrients in the gut, especially fats, are regulated by energy states, and may mediate action of the ketognic diet (Weinshenker, 2004), with increased levels being released in the brain (Tabb et al, 2004). It has also been suggested that calorie restriction alone may underlie the anticonvulsant mechanism of the diet; this reduced seizure susceptibility in mice independent of any changes in ketosis (Greene et al, 2003).

Polyunsaturated fatty acids have been shown to be more ketogenic than saturated fats or oils (Fuehrlein et al, 2004), and a diet enriched in the essential fatty acids linoleate and α-linolenate more ketogenic than other long chain fats or oils (Cunnane, 2004). The ketogenic diet has also been shown to raise plasma levels of

free fatty acids released from adipose tissue (Cunnane et al, 2004). Could these essential fatty acids be directly protective against seizures? If so, could this explain some of the anecdotal differences between the two dietary protocols that have been previously reported? The MCT protocol has a theoretical risk of being considerably lower in essential long chain fatty acids due to the large percentage of fat energy provided by the MCT; in contrast, many classical diets will contain much higher amounts, particularly if aiming for a healthier balance of fatty acids within the overall fat provision. Despite limited information in the literature, in our trial, children on the MCT diet were supplemented with essential fatty acids if continuing beyond 3 months, to ensure no risk of low intakes. Clearly more investigation needs to be done into these specific requirements on the MCT diet.

There are a number of limitations in the data analysis for this study. Total numbers of daily seizures were used, despite more detailed records being kept of numbers of six individual seizure types. A more complex seizure sub-group analysis is aimed for in the future, yielding more detailed results on how different seizure types may respond. Absences seizures are included in the current analysis; however, these are difficult to record accurately without accompanying 24-hour EEG data. The analysis also was based only on the daily seizures in the 28 days before each time point, and did not take into account the numbers over the whole of the 3 or 6-month period; this is hoped for at the time of a full seizure sub-type analysis. The use of parental or carer seizure records will run the risk of subjective errors; it is hoped that even if present, within-person recording would be consistent over the study period. However it is likely that recording improves with practice over a period of time. The fact that percentage of baseline seizures increased to 137% after 3 months in the control group supports this theory; this may have led to an underestimation of the

benefit of the diet over time. Analysis of the EEG results will be independent of any subjective errors, and would be expected to correlate closely with clinical outcome, as seen in the largest study on the diet to data (Kang et al, 2005). However, early results on 48 children from our study suggest this may not be the case (Mills et al, 2006), with EEG being a poor indicator of apparent seizure response. Further results are awaited.

The scientific weight of this study would also have been improved by an intention to treat analysis. This was not possible, as the children who either did not start treatment, or who dropped out before 3 months did not keep on-going seizure records. It would have been very difficult for these parents or carers to have motivation to continue records, but in retrospect, inclusion of this data would have been preferable.

Our study showed a high non-start and drop out rate. After initial outpatient assessment, 145 children were randomized into the trial. Twenty subsequently did not start the treatment, for a variety of reasons; in five children this decision was made after the diet had been calculated and a comprehensive education program completed. In 25 additional children, the treatment was terminated before the 3-month trial period. Although in many cases this was due to intolerance or increased seizures, six children were withdrawn because of parental unhappiness with the necessary dietary restrictions. Of the initial 145, only 100 (69%) actually completed 3 months on the diet. A further six did not complete seizure records as instructed; data was available for analysis on 94. This high non-start and drop out rate was difficult to predict, but has important implications for the careful use of scarce dietetic resources because of the time consuming nature of initial ketogenic calculations and monitoring. Although it has been suggested that non-medical reasons for discontinuing the diet are as

common as medical reasons (Lightstone et al 2001), no other literature on the ketogenic diet has reported similar results prior to diet start or in the early stages of treatment.

The use of a randomization process to allocate children to one of the two dietary regimens, and to either control or non-control, using a minimizing method to account for age group and treatment location, will avoid any selection bias between the study groups. The minimizing process did not control for gender; there were a greater proportion of boys than girls in the diet group as compared with the control group, and in the classical group as compared with the MCT group; there is no evidence that this would have any influence on seizure control. The study would be improved by a double blind randomization process, as recommended by Glauser et al (2006) for all Class I or II scientific evidence. It would have been impossible to blind the parents, carers or child receiving treatment, due to the nature of this being a prescribed diet that closely involved their co-operation. Most families were fully aware of the different types of diet, and what type of food intake they included, usually before even being seen at the initial assessment clinic. In this study, the dietitian prescribing the diets was also very involved in data collection, so would be unable to be blinded. An improvement, that was not possible due to study resources, would have been to have an independent person, who was blinded as to group allocation, doing all the data collection and analysis.

Despite these limitations, this study has been clearly able to demonstrate in a randomized controlled trial that the ketogenic diet is efficacious in treating children with intractable epilepsy, and that both classical and MCT protocols can be used with success in this group.

APPENDIX

Table A3.1. Seizure recording charts – seizure types

Seizure type		Description
1	Absence/atypical absence	
2	Myoclonic	
3	Atonic	
4	Tonic	
5	Tonic-clonic	
6	Partial	

Table A3.2. Seizure recording charts – daily monitoring

Seizure monitoring

Week..... **Start Date.....**

Date	Day	Seizure Type						Ketones		Comments
		1	2	3	4	5	6	AM	PM	
	Sun									
	Mon									
	Tues									
	Wed									
	Thurs									
	Fri									
	Sat									
	Total									

Week..... **Start Date.....**

Date	Day	Seizure Type						Ketones		Comments
		1	2	3	4	5	6	AM	PM	
	Sun									
	Mon									
	Tues									
	Wed									
	Thurs									
	Fri									
	Sat									
	Total									

Table A3.3. Efficacy data recorded for all children

Study no	Diet (1=classical 2=mct)	Sex (1=male 2=female)	Control	Age group	Centre (H=hospital R=residential)	Syndrome	Syndrome group	No. of baseline drugs	% baseline seizures Control	3 mo	6 mo	12 mo	Gradient of best fit of serial seizure data
1	2	2	Y	2	H	Unspec symp gen	Symp gen	2	106.3	29.41	117.65	.	.
2	2	1	N	1	H	Unspec symp multifoc	Symp focal	2	.	155.1	300	.	.
3	1	2	Y	1	H	SMEI	.	3	170	129.41	.	.	.
4	2	1	Y	2	H	Lennox-Gastaux	Symp gen	3	95.71	68.66	69.9	196.5	8.882
5	1	1	N	1	H	Infantile spasms	Symp gen	3	.	39.67	42.59	32.78	-4.585
6	2	2	N	2	H	Structural brain malf	Symp focal	2	.	136.14	140.59	.	.
7	1	1	Y	3	H	Lennox-Gastaux	Symp gen	1	209.2	11.28	8.89	0	-6.904
8	1	2	Y	2	H	Myoclonic absence	Symp gen	2	.	.	.	.	.
9	2	2	Y	2	H	Unspec symp gen	Symp gen	2	155.3	.	.	.	.
10	2	2	Y	3	R	Lennox-Gastaux	Symp gen	3	151.2	47.95	71.85	42.06	-3.747
11	1	1	N	1	H	Infantile spasms	Symp gen	3	.	5.35	51.82	123.7	4.279
12	1	1	N	1	H	Degenerative	.	4	.	.	.	.	.
13	2	2	N	2	R	Myoclonic absence	Symp gen	4	.	.	.	.	.
14	1	1	Y	2	H	Unspec symp gen	Symp gen	2	192.3	107.14	.	.	.
15	2	1	N	1	H	Unspec symp gen	Symp gen	3	.	.	.	.	.
16	1	2	Y	3	H	Myoclonic unspec	Symp gen	2	100	56.1	60.98	52.44	-3.194
17	1	1	N	1	H	Structural brain malf	Symp focal	2	.	13.87	6.03	1.57	-6.871
18	2	1	N	2	H	Myoclonic astatic	.	2	.	.	.	.	.
19	1	1	Y	2	H	Structural brain malf	Symp focal	2	108.9	.	.	15.08	-7.077
20	2	2	Y	1	H	Structural brain malf	Symp focal	2	.	76.83	30.76	4.21	-8.208
21	1	1	N	2	H	Lennox-Gastaux	Symp gen	2	.	24.73	13.44	40.32	-3.789
22	2	2	Y	2	H	Structural brain malf	Symp focal	2	96.8	90.46	.	.	.
23	2	1	N	1	H	Structural brain malf	Symp focal	3	.	48.74	61.78	70.37	-1.439
24	2	2	Y	3	H	Myoclonic astatic	.	1	62.97	.	.	.	.
25	2	1	N	2	H	Myoclonic absence	Symp gen	3	.	70.84	74.46	.	.

26	1	1	N	1	H	Unspec symp multifoc	Symp focal	2	.	79.41	.	.	.	.
27	1	2	Y	2	H	Unspec symp gen	Symp gen	3	109.3	.	.	.	.	.
28	1	2	Y	3	R	Lennox-Gastaux	Symp gen	3	.	.	.	.	.	.
29	1	1	N	2	H	Structural brain malf	Symp focal	3	.	.	.	.	.	.
30	2	1	Y	1	H	Unspec symp multifoc	Symp focal	2	56	385.71	.	.	.	.
31	1	1	Y	3	R	Structural brain malf	Symp focal	2	41.58	61.29	.	.	.	.
32	2	2	Y	3	R	Unspec symp multifoc	Symp focal	2	.	.	.	.	.	.
33	1	1	N	1	H	Lennox-Gastaux	Symp gen	3	.	125.7	.	.	.	.
34	1	2	Y	1	H	Unspec symp multifoc	Symp focal	2	496.6	.	.	.	.	.
35	2	1	N	1	H	Unspec symp gen	Symp gen	2	.	4.74	79.09	.	.	.
36	2	1	Y	2	H	SMEI	.	0	60.67	72.22	.	.	.	.
37	2	2	Y	1	H	Lennox-Gastaux	Symp gen	3	233.2	46.83	67.18	31.29	-4.683	
38	2	2	N	3	R	Unspec symp gen	Symp gen	2	.	142.48	.	.	.	.
39	2	1	N	2	H	Lennox-Gastaux	Symp gen	2	.	13.56	12.29	0	-6.937	
40	1	1	N	1	H	Lennox-Gastaux	Symp gen	3	.	30.3	18.18	54.55	-2.684	
41	1	1	Y	2	H	Unspec symp focal	Symp focal	1	28.21	.	.	.	.	.
42	2	2	N	1	H	Unspec symp focal	Symp focal	1	.	40.82	.	.	.	.
43	1	1	Y	1	H	Infantile spasms	Symp gen	0	.	.	.	.	.	.
44	2	2	N	1	H	Structural brain malf	Symp focal	3	.	.	.	.	.	.
45	1	2	N	1	H	Infantile spasms	Symp gen	2	.	200	.	.	.	.
46	1	1	N	2	R	Atypical absence	Symp gen	3	.	112.43	88.16	.	.	.
47	2	1	Y	1	H	Myoclonic astatic	.	4	116.1	.	.	.	.	.
48	1	2	Y	1	H	Myoclonic absence	Symp gen	1	68.3	54.99	98.77	83.19	-0.167	
49	2	2	Y	2	H	Unspec symp multifoc	Symp focal	3	81.93	132	.	.	.	.
50	1	2	Y	1	H	Early myoclonic enceph	Symp gen	2	575	7.14	23.37	.	.	.
51	1	1	N	3	H	ESES	Symp gen	3	.	.	.	.	.	.
52	2	1	Y	1	H	Myoclonic unspec	Symp gen	1	214.5	96.62	238.89	158	6.388	
53	2	2	N	1	H	Lennox-Gastaux	Symp gen	3	.	46.56	16.82	137.3	3.934	
54	2	2	N	3	H	Structural brain malf	Symp focal	3	.	59.26	.	.	.	.
55	1	1	N	2	H	Unspec symp gen	Symp gen	2	.	26.5	18.36	9.93	-6.398	

56	2	1	Y	1	H	Unspec symp gen	Symp gen	3	.	.	.	.	.
57	1	2	Y	1	H	Unspec symp multifoc	Symp focal	4	57.33	54.11	0.74	50.42	-3.884
58	2	1	Y	1	H	Structural brain malf	Symp focal	2	178.3	93.59	.	.	.
59	1	2	N	2	H	Unspec symp focal	Symp focal	3	.	35.07	21.71	0	-7.462
60	1	1	Y	2	R	Myoclonic unspec	Symp gen	3	93.48	58.14	.	.	.
61	1	2	Y	1	H	Myoclonic unspec	Symp gen	2	93.72	57.75	47.01	43.75	-4.119
62	1	1	N	3	H	SMEI	.	0	.	83.2	103.2	.	.
63	2	2	N	3	R	Unspec symp focal	Symp focal	3	.	.	.	.	.
64	2	1	Y	2	H	Myoclonic unspec	Symp gen	3	.	31.67	0.91	18.9	-5.943
65	2	2	N	2	H	Myoclonic astatic	.	3	.	.	.	.	.
66	2	1	N	2	R	Unspec symp focal	Symp focal	3	.	29.31	19.83	26.29	-5.062
67	2	2	N	1	H	Lennox-Gastaux	Symp gen	3	.	43.36	45.76	44	-3.698
68	1	1	Y	1	H	Infantile spasms	Symp gen	2	128.7	.	.	.	.
69	2	1	Y	3	H	Structural brain malf	Symp focal	1	100	.	.	.	.
70	1	1	N	1	H	Infantile spasms	Symp gen	2	.	.	.	.	.
71	1	1	N	3	H	Structural brain malf	Symp focal	3	.	83.67	72.96	.	.
72	1	2	Y	2	H	Atypical absence	Symp gen	0	.	.	.	.	.
73	2	1	N	2	H	Myoclonic absence	Symp gen	1	.	66.29	90.29	72	-1.529
74	2	1	N	1	H	SMEI	.	2	.	.	.	.	.
75	1	2	N	1	H	Myoclonic astatic	.	2	.	0	0	0	-6.667
76	2	1	Y	2	H	Atypical absence	Symp gen	3	113.4	12.85	.	0	-6.74
77	1	2	N	2	H	Unspec symp focal	Symp focal	2	.	91.26	112.24	.	.
78	1	2	N	2	H	Structural brain malf	Symp focal	1	.	.	.	.	.
79	1	1	N	1	H	Myoclonic unspec	Symp gen	2	.	90.48	.	.	.
80	1	2	N	1	H	Structural brain malf	Symp focal	2	.	46.3	2.84	0	-7.962
81	1	1	Y	2	H	SMEI	.	1	.	.	.	.	.
82	2	1	N	1	H	Myoclonic astatic	.	2	.	15.98	7.01	14.61	-5.804
83	2	1	Y	1	H	SMEI	.	2	294.1	52	84	.	.
84	1	1	Y	2	H	Myoclonic unspec	Symp gen	2	.	38.17	21.5	26.17	-5.309
85	2	2	Y	1	H	Unspec symp focal	Symp focal	3	81.06	93.46	103.74	42.99	-4.664

86	2	1	N	1	H	Infantile spasms	Symp gen	3	.	82.48	.	.	.	.
87	1	2	Y	2	H	Unspec symp focal	Symp focal	0	.	.	.	.	.	.
88	1	1	Y	1	H	Unspec symp focal	Symp focal	3	84.78	163.04	.	.	.	.
89	2	2	N	1	H	Myoclonic unspec	Symp gen	2	.	40.54	62.31	100.1	1.35	
90	2	2	Y	1	H	Structural brain malf	Symp focal	2	82.33	71.87	.	.	.	
91	2	2	N	2	H	Structural brain malf	Symp focal	3	.	28.57	42.86	61.14	-1.834	
92	1	2	Y	2	H	Unspec symp multifoc	Symp focal	4	38.32	41.84	10.28	.	.	
93	2	2	N	1	H	Infantile spasms	Symp gen	1	.	37.29	10.57	6.04	-7.114	
94	2	1	Y	2	H	Unspec symp gen	Symp gen	3	119.1	113.21	100	137	2.792	
95	2	1	Y	1	H	SMEI	.	3	118.1	51.2	5.24	0	-8.08	
96	1	2	N	1	H	Unspec symp gen	Symp gen	2	.	.	.	.	.	.
97	1	1	Y	1	H	Infantile spasms	Symp gen	4	135	72.12	74.94	71.41	-1.893	
98	1	2	N	2	H	Unspec symp focal	Symp focal	1	.	125	46	.	.	
99	2	2	N	1	H	Unspec symp gen	Symp gen	3	.	41.61	64.54	.	.	
100	2	1	Y	1	H	Myoclonic astatic	.	3	121.7	70.7	.	.	.	
101	1	2	Y	1	H	Infantile spasms	Symp gen	2	.	.	.	.	.	.
102	1	1	N	1	H	Structural brain malf	Symp focal	3	.	.	.	.	.	.
103	2	2	N	2	H	Unspec symp focal	Symp focal	2	.	29.48	55.97	.	.	
104	1	1	Y	1	H	Unspec symp focal	Symp focal	3	444	61.26	32.43	26.13	-5.868	
105	2	1	Y	2	H	Unspec symp gen	Symp gen	1	.	.	.	.	.	.
106	1	2	Y	2	H	Structural brain malf	Symp focal	1	87.25	82.78	.	.	.	
107	2	1	Y	1	H	Infantile spasms	Symp gen	1	.	.	.	.	.	.
108	1	2	N	2	H	Unspec symp gen	Symp gen	2	.	.	.	.	.	.
109	2	1	N	3	H	Structural brain malf	Symp focal	3	.	56.63	45.41	23.69	-5.822	
110	1	2	N	1	H	Unspec symp multifoc	Symp focal	1	.	83.35	117.3	.103.0 0	0.898.	
111	2	2	N	2	H	Unspec symp gen	Symp gen	1	.	.	.	.	.	.
112	1	1	Y	3	H	Unspec symp focal	Symp focal	0	100	77.48	.	.	.	
113	2	1	Y	3	H	Structural brain malf	Symp focal	2	36.71	24.14	24.14	.	.	
114	2	2	Y	2	H	Unspec symp gen	Symp gen	3	156.6	62.89	73.88	.	.	
115	1	1	N	2	H	Unspec symp gen	Symp gen	3	.	43.86	23.17	.	.	

116	1	2	N	1	H	Degenerative	.	4	.	.	.	.	.	.
117	1	1	N	1	H	Structural brain malf	Symp focal	4	.	.	.	.	.	.
118	2	2	N	1	H	Unspec symp gen	Symp gen	4	.	.	.	.	.	.
119	2	1	Y	1	H	Unspec symp gen	Symp gen	3	.	58.12	.	.22.00		-5.926.
120	2	1	Y	1	H	Structural brain malf	Symp focal	4	.	.	.	.	.	.
121	1	2	N	2	H	Degenerative	.	3	.	.	.	.	.	.
122	1	2	N	2	H	Unspec symp focal	Symp focal	3	.	75.76	113.64	.63.06		-2.344.
123	2	1	N	1	H	Lennox-Gastaux	Symp gen	2	.	96.61	81.36	.93.94		-0.600.
124	1	1	Y	2	H	Unspec symp gen	Symp gen	2	.	.	.	.	.	.
125	1	1	Y	2	H	Lennox-Gastaux	Symp gen	3	.	.	.	.	.	.
126	2	2	N	1	H	Childhood absence	.	1	.	.	.	.	.	.
127	2	1	N	3	H	Childhood absence	.	2	.	.	.	.	.	.
128	2	1	Y	2	H	Unspec symp focal	Symp focal	1	.	.	.	.	.	.
129	1	1	Y	3	H	Structural brain malf	Symp focal	2	59.87	113.83	.	.	.	.
130	2	2	N	2	H	Unspec symp focal	Symp focal	2	.	74.4	.	.	.	.
131	1	2	Y	2	H	Unspec symp multifoc	Symp focal	3	121.7	.	.	.	.	.
132	2	2	Y	2	H	Lennox-Gastaux	Symp gen	3	.	.	.	.	.	.
133	1	1	N	1	H	ESES	Symp gen	3	.	3.52	.	.	.	.
134	2	2	N	1	H	Unspec symp multifoc	Symp focal	4	.	61.59	.40.64	.26.60		-5.759.
135	2	2	Y	2	H	Myoclonic astatic	.	3	50	146.15	.	.	.	.
136	1	1	N	2	H	Myoclonic absence	Symp gen	3	.	27.62	.62.86	.	.	.
137	1	2	Y	2	H	Unspec symp multifoc	Symp focal	2	87.87	18.5	.	.	.	.
138	1	2	N	2	H	Unspec symp multifoc	Symp focal	2	.	2.07	2.07	.0.00		-6.706.
139	1	2	Y	1	H	Structural brain malf	Symp focal	3	.	.	.	.	.	.
140	1	1	N	1	H	Unspec symp gen	Symp gen	2	.	175.61	.160.53	.100.6 6		-1.527.
141	2	2	Y	1	H	Unspec symp gen	Symp gen	2	.	.	.	.	.	.
142	1	1	Y	2	H	Myoclonic absence	Symp gen	1	.	.	.	.	.	.
143	2	2	Y	2	H	Unspec symp multifoc	Symp focal	5	196	0.00	.0.00	.0.00		-6.667.
144	1	2	N	3	H	Structural brain malf	Symp focal	3	.	101.54	.	.	.	.
145	2	1	N	2	H	Structural brain malf	Symp focal	2	.	22.69	.59.44	.	.	.

Table A3.4. Blood ketone levels recorded for all children from whom results available

Study no.	Diet (1=classical, 2=mct)	Beta-hydroxy butyrate (mmol/l)				Acetoacetate (mmol/l)			
		0 mo	3 mo	6 mo	12 mo	0 mo	3 mo	6 mo	12 mo
1	2	0.07	.	5.79	.	.	.	.	.
2	2	0.05	0.58	3.27	1.76	0.036	0.277	1.230	0.826
3	1	.	5.60	3.21	.	.	1.561	1.512	.
4	2	0.05	1.93	2.20	4.83	0.030	0.652	0.605	1.311
5	1	0.19	6.48	5.25	6.06	0.031	1.949	1.866	1.728
6	2	0.05	1.54	2.64	.	0.030	0.487	0.675	.
7	1	0.86	5.88	5.55	3.66	0.192	1.349	1.229	0.676
10	2	0.05	1.04	2.40	2.16	0.008	0.256	0.805	0.536
11	1	0.05	2.58	4.86	4.05	.	1.618	1.852	1.711
14	1	0.05	0.11	.	.	0.045	0.099	.	.
16	1	0.05	3.50	4.17	3.27	0.030	1.170	1.454	1.233
17	1	0.05	3.96	3.36	3.60	0.030	1.098	1.433	1.170
19	1	0.05	4.48	3.81	1.42	0.034	1.155	1.172	0.359
20	2	0.05	1.68	2.42	4.32	0.031	0.793	0.631	0.966
21	1	0.05	4.29	4.28	4.59	0.030	1.046	1.222	0.431
22	2	0.05	1.21	.	.	0.030	0.481	.	.
23	2	0.05	6.48	4.48	6.06	0.030	1.040	0.675	0.851
25	2	0.05	0.90	1.17	.	0.030	0.524	0.432	.
26	1	0.05	3.57	.	.	0.033	1.560	.	.
30	2	0.05	2.70	.	.	0.030	0.684	.	.
31	1	0.05	1.57	.	.	0.030	.	.	.
33	1	0.05	6.88	.	.	0.030	1.229	.	.
35	2	0.05	2.88	3.21	.	0.047	.	0.620	.
36	2	0.05	0.05	.	.	0.032	0.030	.	.

37	2	0.21	4.92	6.87	9.20	0.078	1.974	1.164	1.806
38	2	0.05	0.96.	.		0.030.	.	.	
39	2	0.05	3.03	3.30.		0.055	0.671	0.586.	
40	1	0.07	6.85	6.63	8.28	0.039	1.276	1.453.	
42	2	0.06	3.81.	.		0.035	0.622.	.	
45	1	0.08	3.45.	.		0.110	0.615.	.	
46	1	0.05	4.35	4.95.		0.070	1.202	1.313.	
48	1	0.05	3.66	5.70	5.22	0.034	1.155.		1.444
49	2	0.05	1.62.	.		0.085	0.122.	.	
50	1	0.05	5.37	5.10	1.05	0.037	1.238	1.872	0.260
51	1	0.05	3.24	2.22.		0.032	1.561	1.012.	
52	2	0.05	2.23.		9.65	0.043	0.509.		1.288
53	2	0.05	3.33	2.31.		0.062	0.923	0.615.	
54	2	0.05	1.70.	.		0.030	0.406.	.	
55	1	0.08	3.99	1.99	1.87	0.034.		0.564	0.615
57	1	. .		3.27	4.23.	.		1.434	1.418
59	1	0.15	6.60	4.98	5.25	0.030	1.850	1.618	1.774
60	1	0.05	1.27.	.	.		0.673.	.	
61	1	0.05.		5.19.		0.031.		1.646.	
62	1	0.05	4.53.	.		0.039	1.204.	.	
64	2	0.13	4.41	3.02	0.10	0.030	1.017	0.602.	
66	2	0.05.		2.46	2.38	0.036	0.552	0.773.	
67	2 .		2.03	1.99	0.86.		0.234	0.079	0.143
71	1	0.05	3.20	3.96.		0.030	1.031	0.952.	
73	2	0.07	6.48	3.70	3.99	0.057	2.004	0.981.	
75	1	0.05	6.63	6.84.		0.031	1.882	1.561.	
76	2	0.05.		0.51	0.88	0.090.		0.130	0.180
77	1	0.05	6.90	2.50.		0.030	1.116	1.094.	
79	1	0.05	1.84.	.		0.033	0.033.	.	
80	1	0.05	2.76	3.48.		0.050.		1.495	1.249

82	2	0.46	2.79	6.39	.	0.211	1.227	1.648	.
83	2	0.09	3.66	3.90	.	0.074	1.225	.	.
84	1	0.05	1.50	.	.	0.038	0.447	0.867	.
85	2	0.05	4.59	.	.	0.030	0.691	.	0.265
86	2	0.07	4.74	.	.	.	1.228	.	.
88	1	0.05	4.08	.	.	.	1.120	.	.
89	2	0.05	2.88	5.80	5.88	0.038	.	1.317	1.124
90	2	0.12	1.80	.	.	0.067	.	.	.
91	2	0.05	2.28	4.08	.	0.035	0.648	.	.
92	1	0.05	3.22	2.25	.	.	1.215	0.962	.
93	2	0.05	.	0.38	.	0.030	.	.	0.162
94	2	0.06	2.43	1.06	0.37	0.031	0.776	0.452	0.139
95	2	0.06	8.22	.	6.88	0.045	1.701	.	1.110
97	1	0.05	4.59	5.70	6.27	0.030	1.905	1.312	1.809
98	1	0.05	3.99	2.04	.	0.038	0.176	0.207	.
99	2	0.11	2.04	4.80	.	0.043	0.502	0.391	.
100	2	0.05	3.09	.	.	0.059	0.028	.	.
101	1	0.05	7.32	5.79	.	0.030	.	1.205	.
103	2	0.05	0.76	0.15	0.05	0.057	0.171	0.116	0.095
109	2	.	.	0.31	0.34	.	.	0.096	0.180
110	1	0.10	2.49	1.10	2.75	0.030	0.632	0.183	0.195
112	1	0.05	4.77	.	.	0.030	0.825	.	.
113	2	0.05	1.39	.	.	.	.	.	.
114	2	0.05	3.21	0.40	2.94	.	0.990	0.198	0.859
115	1	0.05	4.65	4.44	4.92	.	1.935	1.198	2.150
122	1	.	2.65	.	3.51	.	.	0.643	1.135
123	2	0.05	2.19	3.18	1.62	0.030	0.427	0.489	0.484
130	2	0.06	2.24	1.89	1.86	.	0.480	0.632	0.600
132	2	0.05	1.42	.	.	0.108	0.484	.	.
133	1	0.28	.	.	4.08	.	.	.	1.719

134	2		0.05	2.12	2.38	4.35	0.041	.	1.017	1.012
135	2		0.05	1.16	1.59	.	0.030	0.294	0.303	.
136	1		0.05	.	5.43	3.42	0.030	0.905	2.180	0.616
137	1	.	.	3.93	.	.	.	1.338	.	.
138	1		0.05	6.69	4.77	6.25	0.030	.	.	.
139	1		0.05	4.20	3.33	4.38	.	1.875	1.131	2.485
140	1		0.05	3.60	3.09	5.07	0.030	1.225	1.267	2.350
141	2		0.22	1.10	.	.	0.570	0.301	.	.
143	2		0.05	4.32	1.68	1.82	.	1.035	0.269	0.453
144	2	.	.	.	3.75	3.55	.	.	0.620	0.981
145	2		0.05	.	0.57	.	0.030	.	0.111	.
151	2		0.05	3.96	5.52	.	.	.	.	.
152	2	.	.	4.26	.	.	.	0.667	.	.
153	2		0.05	.	1.24	.	0.162	.	0.515	.
154	1		0.05	5.50	5.43	.	.	1.458	.	.
155	2	.	.	.	1.39	.	.	.	0.303	.

CHAPTER 4

TOLERABILITY OF THE KETOGENIC DIET

Contents

4.1 Introduction

The recording of how the classical and MCT ketogenic diets are tolerated is an important part of the assessment of their role in the treatment of children with drug-resistant epilepsy. A diet may be extremely efficacious in seizure control, but if a child has problems with tolerance that cannot be resolved by either dietary changes or additional treatments, they may be unable to continue on the regime for any length of time. Although many tolerance problems will manifest themselves while the diet is being commenced or during the first few weeks, other complications may be later in onset.

The ketogenic diet has traditionally been initiated during an inpatient stay in hospital, after an initial period of fasting, and often a fluid restriction. This has been challenged in recent studies, all involving the classical diet (Table 4.1).

Table 4.1 Summary of studies comparing ketogenic diet (KD) initiation protocols

Authors	No	Age	Study Design	In/outpatient diet initiation	Initiation protocol*	Results
Wirrell et al, 2002	14	1.0 yrs – 16.8 yrs, mean = 63 mo	General retrospective review, all non-fasted	6 outpatients, 8 inpatients	Full calories, starting at 1:1 – 2:1 ratio KD, increasing to 3:1 – 4:1 ratio KD over 3-4 days No fluid restriction or fasting	-Time to ketosis (inpatient data only) same as other reported results of fasted children -Efficacy similar to other reported results of fasted children -No problems with outpatient initiation
Kim et al 2004	124 (fasting = 83, non fasting = 41)	Fasting, mean = 5.3 yrs; Non-fasting, mean = 5.3 yrs	Comparative retrospective review, comparing fasted and non-fasted groups	All inpatients	Fasted group: fast until good ketosis, then Day 1= 1/3 4:1 ratio KD, Day 2 = 2/3 4:1 ratio ketogenic diet; Day 3 = full 4:1 ratio KD Non-fasted: Full calories, Day 1= 1/3 high fat diet, 2/3 normal diet; Day 2 = 2/3 high fat diet, 1/3 normal diet; Day 3 = 4:1 ratio KD No fluid restriction	-Efficacy – no significant difference between groups -No significant difference in time to seizure reduction or significant ketosis -Tolerability and complications – fasted group significantly more dehydrated
Vaisleb et al, 2004	54	22 mo – 12 yrs, mean = 6.6 yrs	Comparative retrospective review, all non-fasted, comparing in- and out-patient initiation groups	37 outpatients 17 inpatients	Full calories, starting at 1.1:1 ratio KD, increasing to 4:1 ratio KD in 5 incremental steps as tolerated No fluid restriction or fasting	-No significant difference in adverse effects on initiation -Outpatient group increased 'long-term' adverse effects -No significant difference in seizure control or cognitive improvement
Bergqvist et al, 2005	48 (24 fasted, 24 gradual start)	1-14 yrs	Randomized controlled trial, comparing fasted and gradual diet initiation groups	All inpatients	Fasted group: Fast until good ketosis (up to 48 hrs), then Day 1= 1/3 4:1 ratio KD, Day 2 = 2/3 4:1 ratio KD; Day 3 = full 4:1 ratio KD Non-fasted: Full calories, Day 1= 1.1 ratio KD, Day 2= 2.1 ratio KD, Day 3= 3.1 ratio KD, Day 4= 4.1 ratio KD Fluid intake based on standard guidelines	-Efficacy – equivalent between 2 protocols -Good ketosis – quicker in fasted group, no difference by end of initiation -Adverse events – milder in non-fasted group -Overall tolerance – better in non-fasted group
Rizutti et al, 2007	46	1.5-17 yrs	Prospective, non-randomized, comparing in-and out-patient groups	23 in-patients 23 out-patients	In-patients: fasted for 24 hours, then 4:1 ratio KD Out-patients: 2:1 ratio KD for 10days, then full diet	-Efficacy and transient complications– no difference between protocols -1 year follow up, no differences in adverse events or metabolic profile

Three studies involved a retrospective data review (Wirell et al, 2002; Kim et al, 2004; Vaisleb et al, 2004); two were prospective, one of which was a randomized controlled trial (Berquist et al, 2005). No differences in dietary efficacy or overall achievement of ketosis were reported between fasted and non-fasted children, and between those initiated in hospital or at home. In some studies using a non-fasting protocol was associated with improved tolerance and fewer adverse effects. One study did note increased unspecified long term adverse effects in the outpatient group (Vaisleb et al, 2004); the authors had no explanation for this, but the long term nature of any problems occurring would make this unlikely to be related to any differences in the initiation protocol, but rather due to the random nature of such events.

There have been many reports of gastro-intestinal intolerance in children following the ketogenic diet. Vomiting, diarrhoea, and abdominal discomfort are frequently reported in children using the MCT protocol, thought to be due to the faster digestion and absorption of this type of fat (Figure 1.2). Studies reporting use of the MCT diet are shown in table 4.2; many do report tolerance problems, in some cases occurring in up to half of children being initiated onto the diet. These problems are not unique to the MCT diet. In a study of 129 children using the classical protocol, Kang et al (2004) reported diarrhoea in 33% and vomiting in 28% of patients during the first four weeks of treatment. Only 3% reported constipation, although this could be more of a problem on the classical diet, due to the very low carbohydrate and high fat intake, and in some cases, low fluid intake. A systematic review of 27 papers that listed adverse events in a total of 1066 children on the diet (Keene, 2006) found a lower incidence of gastro-intestinal problems: vomiting was reported in 5.5% and diarrhoea or constipation in 1.9%. In this review, only 3 children were reported to be on the MCT diet, and 3 of the 27 papers did not state which dietary protocol was used.

Study, year and location	No	Age range	Percent MCT in diet	GI Tolerance
Berman, 1978 (USA)	18	2-17 years	60%	Not stated
Clark & House, 1978 (UK)	13	NS	60%	A problem in some, resolved by slow introduction of oil
Huttenlocher et al, 1971 (USA)	12	2.5-16 years	60% aimed for	5 children – diarrhoea, cramps, vomiting, nausea
Huttenlocher et al, 1976 (USA)	18	18mo-18 years	60%	Not stated
Mak et al, 1999 (Tawain)	13	3yrs2mo – 13yrs	65-70%	Diarrhoea (38.5%), abdominal cramps (15.4%), nausea/vomiting (15.4%)
Ross et al, 1985 (USA)	9	3 mo-13 years	60%	Loose stools (1), vomiting (1)
Schwartz et al, 1989a (UK)	55 children and 4 adults	20 under 5 yrs; 25 aged 5-10 yrs; 9 aged 11-15 yrs, and 5 aged 15-54 yrs	60% or 30% in 'modified diet (n=13)	Nausea, vomiting, abdominal discomfort in approx half of patients while establishing diet
Sills et al, 1986 (UK)	50	2-15 years	60% aimed for	44 tolerated diet; 24 tolerated 60% MCT, 18 tolerated 50-58% MCT, 2 tolerated 45% MCT. Diarrhoea/abdominal pain worse if MCT given without food
Trauner et al, 1985 (USA)	17	12mo – 13 years	60% MCT	3 unable to tolerate due to diarrhoea, vomiting nd abdominal pain. Many of the 17 had bulky, loose stools.

Table 4.2 Studies reporting MCT diet treatment and tolerance

Other reported side effects are less common. Haematological disturbances have been seen in children following the ketogenic diet, both impaired neutrophil function (Woody et al, 1989), and alterations in platelet function, with an increased tendency to bleeding (Berry-Kravis et al. 2001). There have been many reports in the literature of raised serum cholesterol and triglyceride levels in children following the ketogenic diet (Dekaban, 1966; Chesney et al. 1999;Vining, 1996; Delgado et al, 1996; Kwiterovitch, 2003; Keene, 2006), although other studies have not found this to be a problem (Schwartz et al, 1989b; Couch et al. 1999). Other isolated reported problems include cardiac complications (Best et al, 2000), pancreatitis (Stewart et al, 2001; Kang et al, 2004; Lyczkowski et al, 2005), selenium deficiency (Bergqvist et al, 2003), and fatal propofol infusion syndrome (Baumeister et al, 2004)

Renal stones have been frequently reported in about 5% of children on the diet (Hertzberg et al, 1990; Furth et al, 2000; Kielb et al, 2000; Freeman et al. 1998; Sampath et al, 2007), and can be a particular problem in children undergoing concomitant anti-convulsant therapy with carbonic anhydrase inhibitors such as topiramate (Kossoff et al, 2002a). There are also concerns about the increased risk of metabolic acidosis in children on topiramate who commence the ketogenic diet; large decreases in bicarbonate levels have been reported in this group (Wilner et al, 1999; Takeota et al, 2002), and close monitoring is needed, especially during diet initiation.

Using the ketogenic diet with concomitant sodium valproate therapy may cause other problems. In one report of five children who developed serious adverse events while on the diet (Ballaban-Gill et al, 1998), the complications were suggested to be due to interactions with valproate in four of the individuals. However, in a larger retrospective study of 71 children, Lyczkowski et al (2005) found no significant

difference in adverse-event profiles between the valproate group and non-valproate group.

An important part of this randomized controlled trial on the ketogenic diet was to investigate the tolerability of the classical and MCT protocols. The results of this aspect of the study are presented in this chapter.

4.2 Methods

All children taking part in this study were commenced on either a classical or MCT ketgenic diet. The initiation protocol for this study has already been discussed (Chapter 2). Diets were started at home under close telephone supervision, without fasting or fluid restriction. Both classical and MCT protocols were initiated using a gradual step-wise protocol; with an expectation of reaching the full prescription within about 10 days of treatment. Problems with dietary tolerance on commencement were all documented carefully in patient study notes. If any problems did occur, the step-wise incremental increases in either diet ratio (classical diet) or MCT amount (MCT diet) were slowed down to try and alleviate the problem, and maintain the child on dietary treatment.

The aim was for all children to try the diet for a minimum of three months; any drop-outs before this time point were documented, and adverse events noted. At 3, 6 and 12 months, children were reviewed at the hospital, and any adverse events documented. Parents or carers of all children were asked to complete a questionnaire at each of these time points, to record any incidence of gastro-intestinal problems. This questionnaire also enquired about hunger or taste problems, lack of energy and any changes in alertness, awareness or responsiveness (see appendix to chapter 4).

Repeat blood samples were also taken for routine haematology and biochemistry, including cholesterol and triglycerides.

Statistical analysis:

- The Fishers exact test was used to compare the results of this parental/carer questionnaire between the two diet groups
- To examine differences in blood cholesterol and triglyceride levels between children on the classical and MCT diets, mean levels were compared at 3, 6 and 12 months using the unpaired t-test. Within person changes from baseline to each of the time points were compared between the two diets using paired t-tests. Differences in the number of children on each diet defined as having high levels of either cholesterol or triglycerides at each of the time points, as defined by age-appropriate ranges set by the Great Ormond Street Hospital laboratory, were compared using the Fishers exact test.

SPSS software version 13 was used for all statistical analysis.

4.3 Results

Tolerability results were examined in three different time frames. Firstly, problems occurring during the initial commencement and early build up of a diet; secondly, problems that occurred after establishment onto the full dietary prescription, but could not be resolved adequately, resulting in withdrawal from the study; thirdly, problems related to tolerance and side effects occurring at 3, 6 and 12 months, which did not directly cause study withdrawal.

4.3.1 Problems during diet commencement

61 children started a classical ketogenic diet, and 64 children started a MCT ketogenic diet (Figure 3.2), all of which were commenced at home. Five of these children stopped the diet within the first week, before being established on the full diet prescription (table 4.3). Two classical diet children had dramatically increased seizure activity (one symptomatic multifocal, on medications valproate and vigabatrin, and one symptomatic generalized (unspecified), on medications lamotrigine and clobazam). One MCT diet child had severe diarrhoea (symptomatic generalized (unspecified), on keppra), one had extreme drowsiness (symptomatic focal (unspecified), on topiramate, keppra and clobazam), and one had severe vomiting (symptomatic generalized (unspecified), on keppra, topiramate, lamotrigine and clobazam). These numbers are too small for statistical comparisons

Table 4.3. Withdrawals during the first week of treatment.

	Classical diet	MCT diet
Increased seizures	2	0
Diarrhoea	0	1
Extreme drowsiness	0	1
Vomiting	0	1

In addition, during the first few days of the study, two classical diet children attended their local hospital (one needed an admission) because of symptoms relating to excess ketosis and acidosis. Both children had Lennox-Gastaut syndrome, and both were on topiramate, one in combination with gabapentin, and one in combination with clobazam and lamotrigine.

4.3.2 Withdrawals before 3 months

Table 4.4 shows other study withdrawals occurring before the recommended 3-month trial of dietary treatment. Three further children reported greatly increased seizure activity resulting in study withdrawal, two on the classical diet (one structural brain abnormality, on tegretol, and one atypical absence, no medication), and one on the MCT diet. (symptomatic multifocal, on medications valproate and oxycarbemazepine). Two further MCT diet children had severe diarrhoea (one tuberous sclerosis, on topiramate, valproate and vigabatrin, and one SMEI, on phenytoin and stiripentol), and one classical diet child had severe constipation (structural brain abnormality, on topiramate, lamotrigine and clobazam). Despite use of medications to help in all three cases, the diet was discontinued.

Table 4.4. Other diet withdrawals before 3 months

	Classical diet	MCT diet
Increased seizures	2	1
Diarrhoea	0	2
Constipation	1	0
Textural food problems	0	1
Parental unhappiness	2	4
Behavioral food refusal	3	4

Other withdrawals before three months were one child who had pre-existing problems with certain food textures which worsened while on the MCT diet, two classical and four MCT diet children who were withdrawn by parents who were unhappy with the dietary restrictions, and three classical and four MCT diet children who had behavioural feeding problems. Again, these were pre-existing and were worsened by dietary treatment. Statistical comparisons of these other withdrawals before 3 months between the two diets were not possible due to small numbers.

4.3.3 Questionnaire results at 3 months

Questionnaire data was available from 47 classical diet children and 42 MCT diet children at 3 months. Results showed no significant differences in reported side effects between the two diets except increased reports of lack of energy on the classical protocol (table 4.5). In addition, 15 of the 47 classical diet children (32%) and 11 of the 42 MCT diet children (26%) needed medication for constipation after 3 months on diet treatment (p=0.643).

Table 4.5. Reported side effects of the classical and MCT diets at 3 months

Side effect	Numbers (%) reported to have side effects		P value
	Classical diet (n=47)	MCT diet (n=42)	
Vomiting	13 (28%)	11 (26%)	0.876
Diarrhoea	7 (15%)	6 (14%)	1.000
Abdominal pain	5 (11%)	8 (19%)	0.369
Constipation	21 (45%)	14 (33%)	0.288
Lack of energy	17 (36%)	6 (14%)	0.028*
Hunger	12 (26%)	14 (33%)	0.487
Taste problems	10 (21%)	7 (17%)	0.603

**** significant at p<0.05 level***

The questionnaire also asked about changes in alertness, awareness and responsiveness. After 3 months on a diet, 39 of the classical diet group (83%) and 32 of the MCT diet group (76%) were reported to have improved alertness (p=0.443); 39 of the classical diet group (83%) and 30 of the MCT diet group (71%) were reported to have improved awareness (p=0.214); and 39 of the classical diet group (83%) and 31 of the MCT diet group (74%) were reported to have improved responsiveness (p=0.313). Three of the MCT diet group (7%), but none of the classical diet group were reported to have a reduction in alertness (p=0.101); two of the MCT diet group (5%) but none of the classical diet group were reported to have a reduction in

awareness (p=0.220); and one of the classical diet group (2%) and 2 of the MCT diet group (5%) were reported to have a reduction in responsiveness (p=0.600). Of the total 71 children who were reported as having improved alertness, only 34 (48%) had over 50% reduction in baseline seizure numbers at this time point; of the total 69 children who were reported as having improved awareness, only 33 (48%) had over 50% reduction in baseline seizure numbers at this time point; and of the total 70 children who were reported as having improved responsiveness, only 36 (51%) had over 50% reduction in baseline seizure numbers at this time point.

4.3.4 Questionnaire results at 6 months

At 6 months, questionnaire data was available from 25 classical diet children and 32 MCT diet children. There were no significant differences in reported side effects between the two diets (table 4.6). In addition, 11 of the 32 classical diet children (34%) and 10 of the 25 MCT diet children (40%) needed medication for constipation after 6 months on diet treatment (p=0.784).

Table 4.6. Reported side effects of the classical and MCT diets after 6 months

Side effect	Numbers (%) reported to have side effects		P value
	Classical diet (n=25)	MCT diet (n=32)	
Vomiting	9 (36%)	7 (22%)	0.373
Diarrhoea	1 (4%)	4 (13%)	0.372
Abdominal pain	2 (8%)	4 (13%)	0.686
Constipation	12 (48%)	13 (41%)	0.602
Lack of energy	2 (8%)	5 (16%)	0.450
Hunger	6 (24%)	6 (19%)	0.747
Taste problems	4 (16%)	11 (34%)	0.141

At 6 months, 21 of the classical diet group (84%) and 27 of the MCT diet group (84%) were reported to have improved alertness (p=1.000); 22 of the classical

diet group (88%) and 26 of the MCT diet group (81%) were reported to have improved awareness (p=0.717); and 21 of the classical diet group (84%) and 26 of the MCT diet group (81%) were reported to have improved responsiveness (p=1.000). One of the classical diet group (4%) and one of the MCT diet group (3%) were reported to have a reduction in alertness (p=1.000); no children in either group were reported to have a reduction in awareness; and one of the classical diet group (4%) and one of the MCT diet group (3%) were reported to have a reduction in responsiveness (p=1.000). Of the total 48 children who were reported as having improved alertness, 30 (63%) had over 50% reduction in baseline seizure numbers at this time point; of the total 48 children who were reported as having improved awareness, 29 (60%) had over 50% reduction in baseline seizure numbers at this time point; and of the total 47 children who were reported as having improved responsiveness, 28 (60%) had over 50% reduction in baseline seizure numbers at this time point.

4.3.5 Questionnaire results at 12 months

At 12 months, questionnaire data was available from 20 classical diet children and 23 MCT diet children. There were significantly more reports of vomiting in the classical diet group, but no significant differences in other reported side effects between the two diets (table 4.7). Eight of the 20 classical diet children (40%) and 9 of the 23 MCT diet children (39%) needed medication for constipation after 12 months (p=1.000).

Table 4.7. Reported side effects of the classical and MCT diets after 12 months

Side effect	Numbers (%) reported to have side effects		P value
	Classical diet (n=20)	MCT diet (n=23)	
Vomiting	9 (45%)	3 (13%)	0.039*
Diarrhoea	2 (10%)	4 (17%)	0.669
Abdominal pain	2 (10%)	4 (17%)	0.669
Constipation	9 (45%)	9 (39%)	0.763
Lack of energy	2 (10%)	3 (13%)	1.000
Hunger	5 (25%)	4 (17%)	0.711
Taste problems	3 (15%)	5 (22%)	0.704

**** significant at p<0.05 level***

At 12 months, 22 of the classical diet group (96%) and 17 of the MCT diet group (85%) were reported to have improved alertness (p=0.324); 22 of the classical diet group (96%) and 17 of the MCT diet group (85%) were reported to have improved awareness (p=0.324); and 22 of the classical diet group (96%) and 17 of the MCT diet group (85%) were reported to have improved responsiveness (p=0.324). Two of the classical diet group (10%) but none of the MCT diet group were reported to have a reduction in alertness (p=0.210); one of the classical diet group (5%) but none of the MCT diet group were reported to have a reduction in awareness (p=0.465); and no children in either group were reported to have a reduction in responsiveness. Of the total 39 children who were reported as having improved alertness, 26 (67%) had over 50% reduction in baseline seizure numbers at this time point; of the total 39 children who were reported as having improved awareness, 25 (64%) had over 50% reduction in baseline seizure numbers at this time point; and of the total 39 children who were reported as having improved responsiveness, 26 (67%) had over 50% reduction in baseline seizure numbers at this time point.

4.3.6 Other side effects, cholesterol and triglycerides

At the 3-month outpatient visit one classical diet child (infantile spasms, on topiramate, lamotrigine and clobazam) was found to have haematuria. A subsequent renal ultrasound detected debris, indicating risk of stone formation. Following treatment with potassium citrate, the child remained on the diet without any recurrence of the problem. Routine haematology and biochemistry at 3 months showed no significant abnormalities. Cholesterol and triglyceride levels were analyzed in detail, although data was not available at all time points from all children. General trends in levels over the 12-month period, subdivided by diet, are shown in Figures 4.1 and 4.2.

Figure 4.1 Serum cholesterol levels in classical and MCT diet children at baseline, 3, 6 and 12 months.

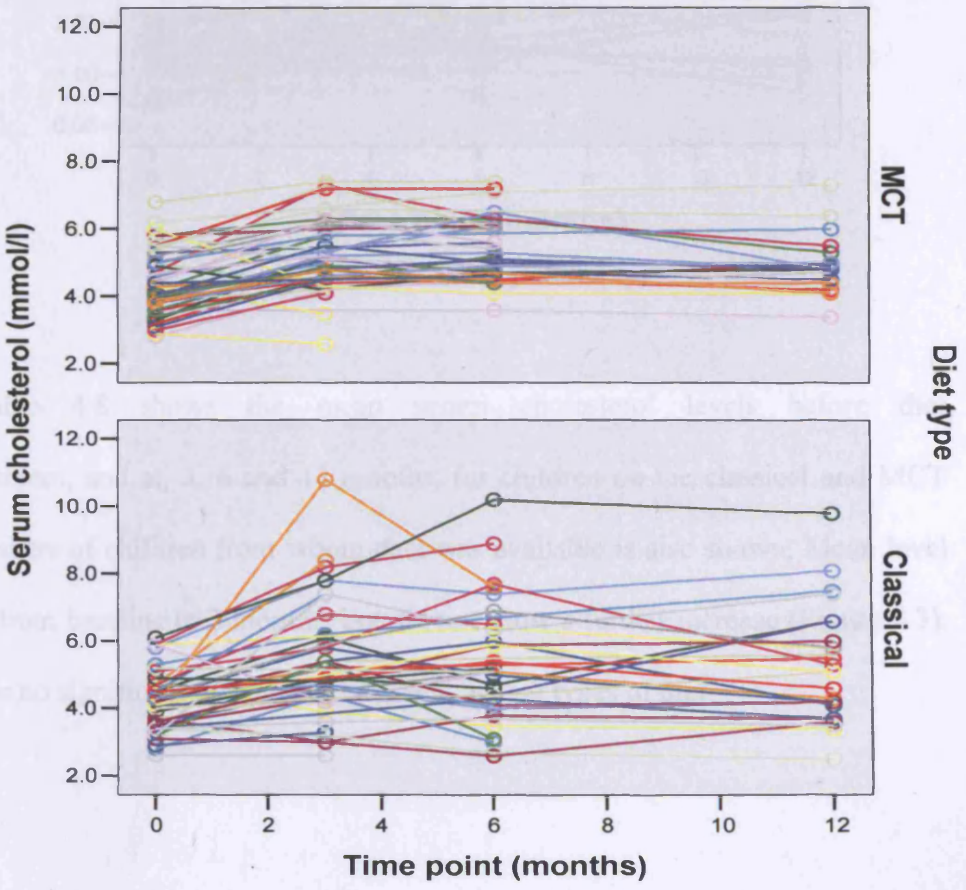


Figure 4.2 Serum triglyceride levels in classical and MCT diet children at baseline, 3, 6 and 12 months

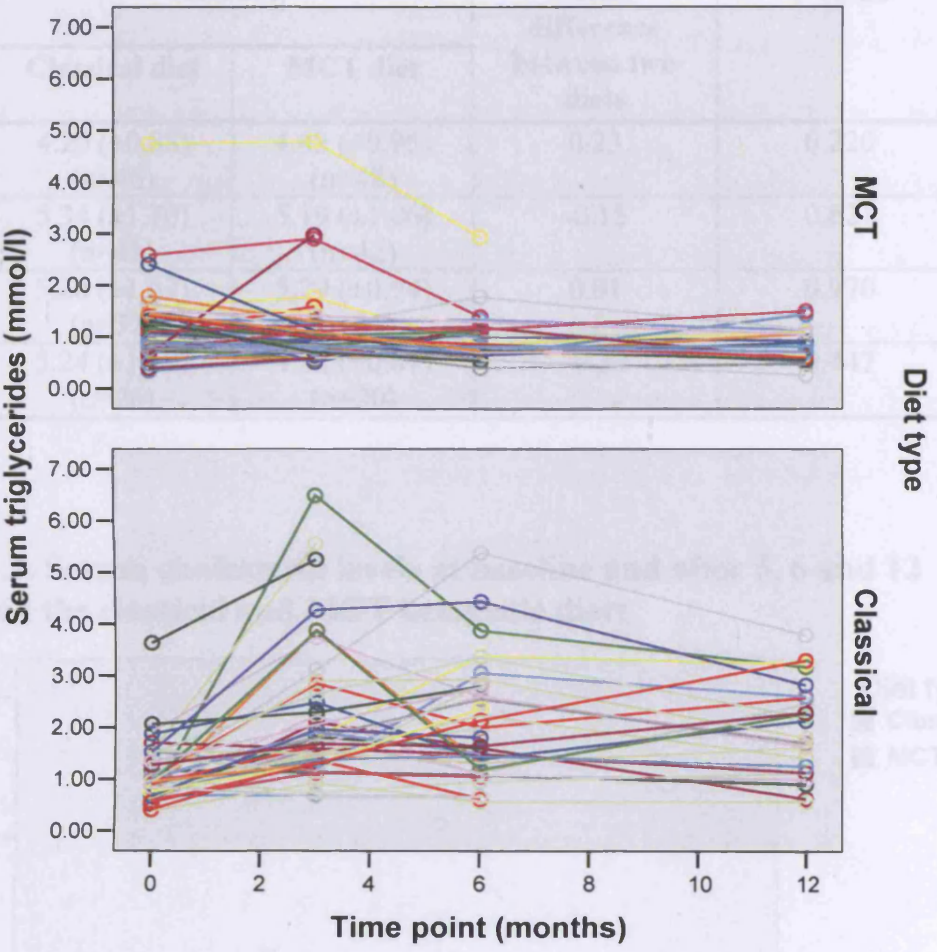


Table 4.8 shows the mean serum cholesterol levels before diet commencement, and at, 3, 6 and 12 months, for children on the classical and MCT diets. Numbers of children from whom data was available is also shown. Mean level increased from baseline to 3 months, but did not show a further increase (Figure 4.3). There were no significant differences between the two types of diet

Table 4.8. Serum cholesterol levels at baseline and after 3, 6 and 12 months on the classical and MCT ketogenic diets

	Mean (±SD) serum cholesterol (mmol/l)		Mean difference between two diets	P value
	Classical diet	MCT diet		
Baseline	4.20 (±0.88) (n=46)	4.43 (±0.95) (n=48)	0.23	0.220
3 mo	5.34 (±1.70) (n=41)	5.19 (±1.06) (n=42)	-0.15	0.621
6 mo	5.28 (±1.67) (n=37)	5.29 (±0.94) (n=35)	0.01	0.970
12 mo	5.24 (±1.69) (n=26)	4.92 (±0.87) (n=20)	-0.32	0.447

Figure 4.3. Serum cholesterol levels at baseline and after 3, 6 and 12 months on the classical and MCT ketogenic diets

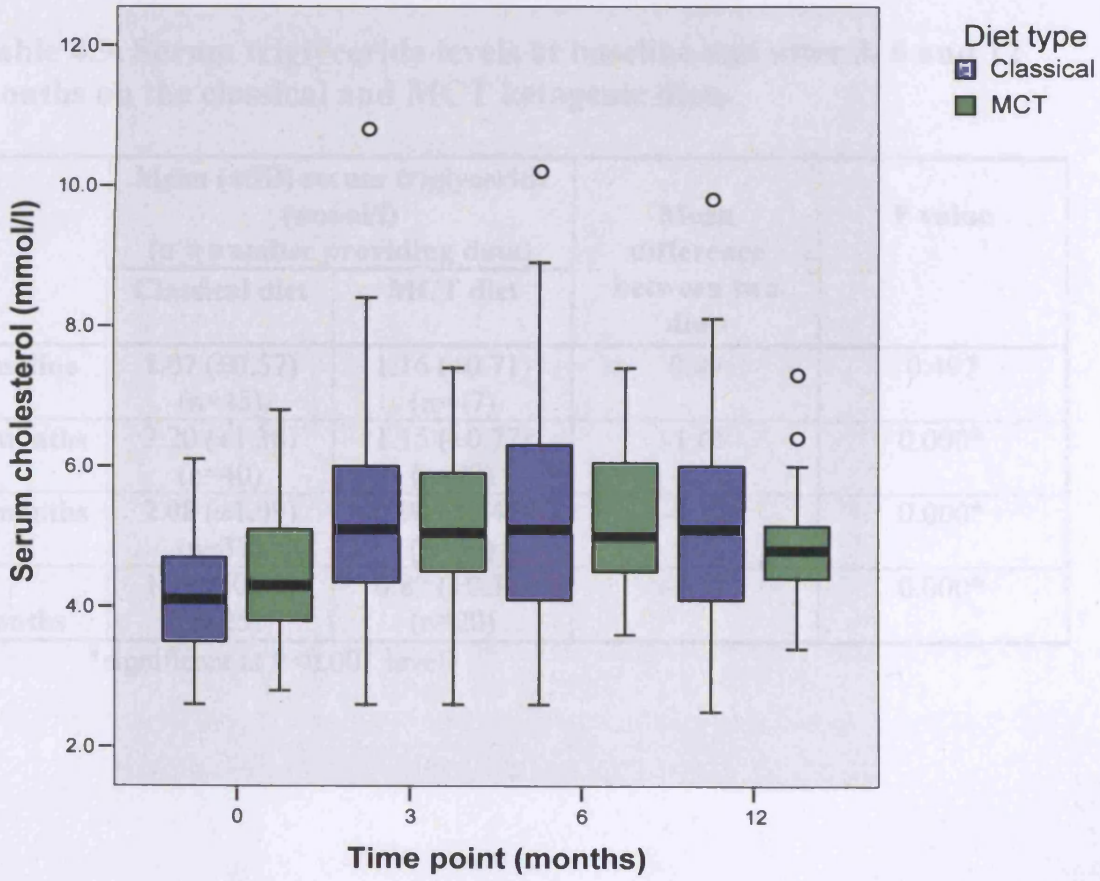


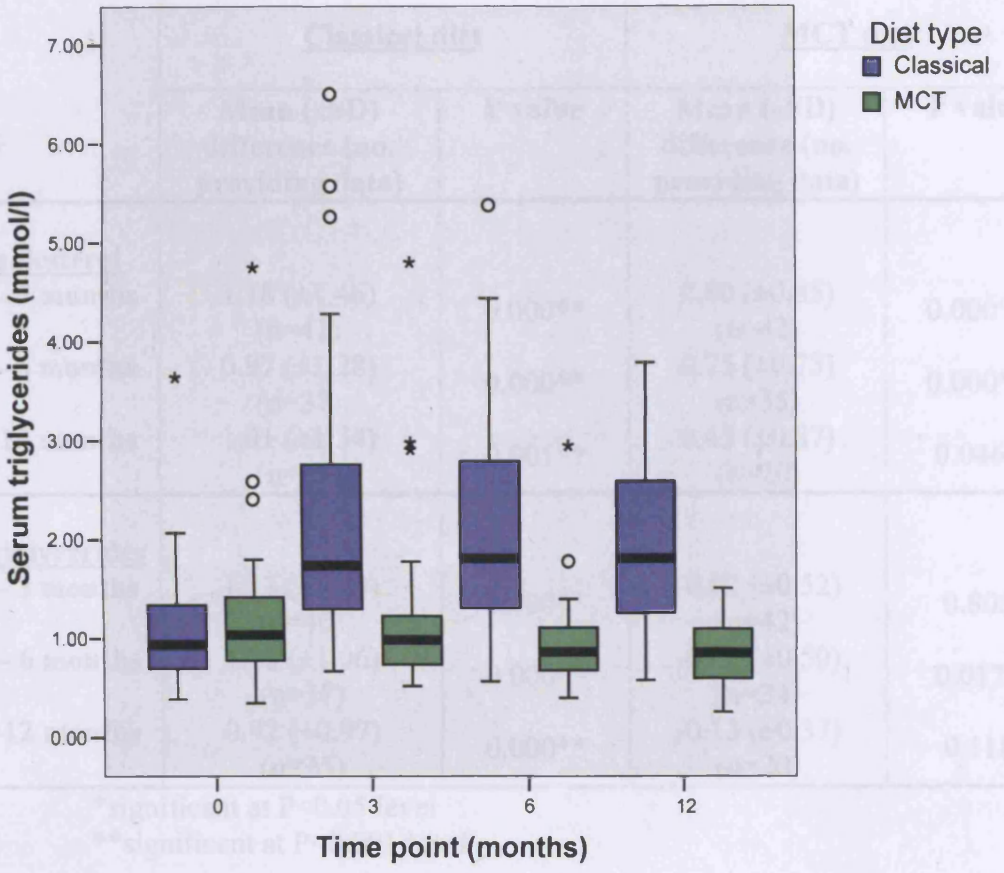
Table 4.9 shows the mean serum triglyceride levels before diet commencement, and at, 3, 6 and 12 months, for children on the classical and MCT diets. Numbers of children from whom data was available is also shown. In the classical diet group, mean level increased from baseline to 3 months, and then stayed around this higher level, however the mean level in the MCT group fell to less than baseline during the 12-month period. This trend is illustrated in Figure 4.4; this plot also shows that there were a number of outlying children on both diets with very high triglyceride levels, this was particularly noticeable in the classical diet group. Whereas there was no significant difference in baseline mean triglyceride level between the two types of diet, after 3, 6 and 12 months this was lower in the MCT group, the difference was highly statistically significant.

Table 4.9. Serum triglyceride levels at baseline and after 3, 6 and 12 months on the classical and MCT ketogenic diets

	Mean (±SD) serum triglyceride (mmol/l) (n = number providing data)		Mean difference between two diets	P value
	Classical diet	MCT diet		
Baseline	1.07 (±0.57) (n=45)	1.16 (±0.71) (n=47)	0.09	0.497
3 months	2.20 (±1.38) (n=40)	1.15 (±0.77) (n=42)	-1.05	0.000*
6 months	2.08 (±1.09) (n=37)	0.96 (±0.46) (n=34)	-1.12	0.000*
12 months	1.98 (±0.88) (n=25)	0.87 (±0.33) (n=20)	-1.12	0.000*

*significant at P<0.001 level

Figure 4.4. Serum triglyceride levels at baseline and after 3, 6 and 12 months on the classical and MCT ketogenic diets



The mean within-person differences between baseline and 3, 6 and 12-month cholesterol and triglyceride levels were computed for children on the classical and MCT diets, and tested for significance. Results are shown in table 4.10. On both diets this significantly increased at all time points for cholesterol; this was also the case for triglycerides in the classical diet group. However the mean within-person difference in triglycerides in the MCT group decreased from baseline to 3, 6 and 12 months; this was just significant at 6 months only.

Table 4.10 Within-person paired differences in serum cholesterol and triglyceride levels in children on classical and MCT diets

	Classical diet		MCT diet	
	Mean (±SD) difference (no. providing data)	**P value**	**Mean (±SD) difference (no. providing data)**	**P value**
Cholesterol				
0 – 3 months	1.18 (±1.46) (n=41)	0.000**	0.80 (±0.85) (n=42)	0.000**
0 – 6 months	0.97 (±1.28) (n=37)	0.000**	0.75 (±0.75) (n=35)	0.000**
0–12 months	1.01 (±1.34) (n=26)	0.001**	0.42 (±0.87) (n=20)	0.046*
Triglycerides				
0 – 3 months	1.13 (±1.25) (n=40)	0.000**	-0.02 (±0.52) (n=42)	0.805
0 – 6 months	1.05 (±1.06) (n=37)	0.000**	-0.22 (±0.50) (n=34)	0.017*
0–12 months	0.92 (±0.97) (n=25)	0.000**	-0.13 (±0.37) (n=20)	0.118

*significant at P<0.05 level
**significant at P<0.001 level

Tables 4.11 and 4.12 show the numbers of children at baseline and after 3, 6 and 12 months on both diets that would be defined as having high serum cholesterol and triglyceride levels, being above the age-appropriate ranges. At baseline, more MCT diet children had raised cholesterol; numbers were similar in both diet groups for triglycerides. After 3, 6, and 12 months, there were no significant differences between the diets in numbers with raised cholesterol levels, both groups showing between 30-40% of children to have a high level at any time point. After 3, 6 and 12 months, there was a highly significant difference between the diets in numbers of children with raised triglyceride levels. Over half of the classical diet group had high levels by 3

months; this increased to over two-thirds by 6 and 12 months. In contrast, numbers with high levels dropped during diet treatment in the MCT group.

Table 4.11. Numbers of children on classical and MCT diets with high serum cholesterol levels at baseline, 3, 6 and 12 months

Time	Number of children with high cholesterol level		P value
	Classical diet	MCT diet	
Baseline	5/46 (11%)	10/48 (21%)	0.262
3 months	16/41 (39%)	15/42 (36%)	0.823
6 months	14/37 (38%)	14/35 (40%)	1.000
12 months	9/26 (35%)	6/20 (30%)	1.000

Table 4.12. Numbers of children on classical and MCT diets with high serum triglyceride levels at baseline, 3, 6 and 12 months

Time	Number of children with high triglyceride level		P value
	Classical diet	MCT diet	
Baseline	11/45 (24%)	11/47 (23%)	1.000
3 months	23/40 (57%)	6/42 (14%)	0.0001*
6 months	23/37 (62%)	2/34 (6%)	0.0001*
12 months	17/25 (68%)	1/20 (5%)	0.0001*

*significant at P<0.001 level

4.4 Discussion

The children in our study were able to start their diets at home, without a fasting period. This will have many advantages for the family. The inconvenience and disruption of a hospital admission can be avoided, as can the risk of potential adverse events caused by starvation. Since commencement of our study, other groups have shown non-fasted children to have better tolerance and fewer adverse events, with no difference in efficacy (Kim et al, 2004; Berquist et al, 2005). However, advocates of hospital admission will argue that it allows a much closer monitoring of

the initiation process. Five of our study children stopped the diet within the first week; two because of increased seizures, one due to extreme drowsiness, one vomiting and one diarrhoea. Could these early withdrawals have been avoided if the children were admitted to hospital, and therefore monitored more closely? In all cases, the families were in very close contact with the ketogenic diet team, and advice was given to try and alleviate the symptoms. It is unlikely that hospital admission would have made any difference to outcome. Indeed, the child who withdrew due to extreme drowsiness was actually at the residential centre for young people with epilepsy, and had round the clock nursing and medical care during this period. In their retrospective review of 54 children, comparing in- and out-patient initiation groups, Vaisleb et al (2004) found no significant difference in adverse events or efficacy between the two groups. However, our study experience has shown that diets started at home do need to have a careful, stepwise fat increase: all classical diets were commenced at a 2:1 ratio, which was increased to 4:1 as tolerated, and the MCT in the MCT diets was also built up slowly.

The advocates of inpatient admission will also argue that it provides a setting for an intensive education program about the diet, including supervised practice in meal preparation. Although this may be the case in a few larger centres that have experience in the ketogenic diet and a well-established initiation program, it is only a theoretical ideal in many other UK hospitals. Many families have found inpatient admissions to be frustrating and lonely, with both ward staff and diet cooks unprepared for the complexities of such a diet, and dietitians only able to give limited time to education due to multiple other work commitments that cannot be put on hold. All parents or carers of children starting the diet in out study were given a full day of teaching, and regular discussions over the phone to reinforce knowledge. Whereas a

teaching program over a longer period of time may have been an advantage, this was not possible due to the constraints of limited staff and bed availability. In most children, it is unlikely that this would have any impact on long-term success of the diet, although in a very small number who have parents or carers who found the mathematical nature of the diet difficult to follow, it may have been an advantage.

During the early stages of the study, two study children did need to attend their local hospital, one requiring admission, due to problems with acidosis and excess ketosis, related to use of the anti-epileptic medication topiramate. Both were following the classical diet; after these episodes, extra care was taken when commencing a child on topiramate onto the classical protocol, ensuring that they stayed on a 2:1 ratio diet for a few days without problems, before increasing the ratio gradually.

The diet was stopped before 3 months in 20 other children; three of these were due to increased seizure activity, two due to diarrhoea and one due to constipation. Although numbers were too small for statistical comparisons, it is of interest that four of the five withdrawals due to increased seizures were on the classical diet, and all three children with excessive diarrhoea were on the MCT diet. There was no obvious link between any of these side effects and either the child's epilepsy syndrome, or anti-epileptic medications. Other withdrawals included problems with the food texture in one child and behavioural eating problems in 7 children; all of which were present prior to the child starting the diet, but worsened by this treatment Six other children were withdrawn from the study by parents who felt unhappy with the restrictions the diet imposed on their child. Following these results, our study group would recommend that in future the initial assessment and screening process should be even more comprehensive, with future inclusion criteria ensuring that children with pre-

existing behavioural feeding problems have these appropriately treated before embarking on a restrictive dietary regimen. The willingness and full understanding of parents and all other important carers to comply with restrictions and monitoring, before commencing treatment, is also paramount, particularly in cases where care is shared between two or more individuals who live in separate locations.

After 3 months of treatment, the main reason for dietary withdrawal was limited efficacy. Although problems with tolerability were still reported, these were not considered severe enough to merit dietary withdrawal if seizure control had significantly improved. Tolerability was assessed by the reports of parents or carers, either over the telephone, or at clinic visits, and by a questionnaire. Although the use of our non-validated questionnaire could be questioned, and obviously this assessment method could be subject to a degree of bias by its subjective nature, it did provide a useful way to serially assess the opinion of parents or carers on tolerance or any side effects. There would be no advantage for any family to over or under report problems, and although questions were asked about any side effects from the diet in the outpatient clinic setting, the written responses to the questionnaire were not discussed at these visits.

The results of this questionnaire do not support the idea that the MCT diet has a worse profile of abdominal side effects. There do seem to be more reports of diarrhoea associated with this protocol after 6 and 12 months, as seen in the early drop-outs. This was not seen at 3 months, and no difference was significant. Reports of abdominal pain were also higher in the MCT group at all time points, again not significant. No more than 20% of any group reported either of these problems at any time point. There was a higher incidence of vomiting; this was reported to have occurred in over one quarter of diet children at 3 and 6 months. By 12 months, the

incidence of vomiting was significantly higher in the classical diet group; 45% of families reported that this had been a problem compared to only 13% of the MCT group. This may be due to the higher overall dietary fat content. Although our results for vomiting are similar to those reported by Kang et al (2004) in their large study of classical diet children, our incidence of diarrhoea was lower. Other studies on the MCT diet (table 4.2) frequently report problems of diarrhoea, nausea, vomiting, and abdominal pain; with the exception of the modified MCT group in the study by Schwartz et al (1989a), all these studies were using 60% of energy from MCT in their diets. Although some children in our study did need this level of MCT to attain good ketosis and optimal seizure control, many others were able to achieve these goals on a lower amount. As discussed in chapter 2, diets were generally commenced on 45% energy as MCT, and this percentage increased as needed. This aimed to provide the best balance between optimal seizure control and acceptable tolerability.

In our study constipation was the most frequently reported side effect, present in 39%, 44% and 42% of children at 3, 6 and 12 months respectively. At 3 months, this was more of a problem on the classical diet, as would be expected due to the reduced amount of carbohydrate and increased total fat content, however by 6 and 12 months, numbers were similar on both diets. This was a much higher incidence that that reported by Kang et al (2004); only 3% of their large group of classical diet children were reported to have this problem after 4 weeks; reasons for this difference are not clear. There are no other literature reports of constipation being a problem on the MCT diet; indeed, this type of fat is often advocated as being of benefit as a treatment for the condition. Our study has shown constipation to be a problem on both types of diet, although fluids were not strictly restricted and fruit and vegetables were encouraged as part of the limited carbohydrate intake wherever possible. Although

constipation was only cited as a reason to stop the diet in the one withdrawal before 3 months, approximately one third of all children were on medication for this problem at any time point.

Other reported side effects in our questionnaire results were a lack of energy, hunger and taste problems. It is not clear why significantly more classical diet children were reported as having a lack of energy at 3 months, with over a third of this diet group reported to have the problem, but this difference was not present later in the study. Hunger was a problem in 29% of children at 3 months; this had fallen to 21% by 6 and 12 months. As growth was monitored carefully during the study, and diet calorie content adjusted to ensure appropriate weight gain, it may be that much of the perceived hunger problem was due to the smaller, higher in fat, portion size rather than actual calorie deficit. There were more reports of taste problems with the classical diet at 3 months, but by 6 months, they were worse in the MCT diet group, with over one third reporting problems. However, the difference was not significant, and our overall results do not support the idea of the MCT diet being more unpalatable. By 12 months, the difference between the two protocols was less noticeable, and while a number of parents using the MCT diet did say that incorporating the MCT into the diet was their main challenge, the use of a range of recipe ideas, and at times using MCT oil rather than the higher volume of Liquigen emulsion, seemed to help.

Our questionnaire additionally enquired about any changes in alertness, awareness and responsiveness on the diet. Results were remarkable: after 3 months, over 75% of children reported improvements in alertness, awareness and responsiveness, this increased to over 80% at 6 months, and over 90% at 12 months. A few children were reported to have a reduction of these skills; this was less than 5%

of the total sample at any time point. There were no differences in changes in alertness, awareness and responsiveness between the two dietary protocols. Whereas it is appreciated that the subjective nature of such a questionnaire may lead to an over-reporting of dietary benefits, and that it was not a validated tool that took the age of the child into account, similar improvements have previously been documented. In 2001, Pulsifer et al reported that mean developmental quotient was significantly improved in 34 children who had been on the classical ketogenic diet for a year, with significant behavioural improvements in attention and social functioning. In a study on parental expectations of dietary benefits, Farasat et al (2005) reviewed 100 parental letters written during dietary initiation regarding their goals of treatment. They found the third most common goal, after seizure or anti-epileptic medication reduction, was improvement in cognition or alertness. Of the 63 families who expected this, 59% achieved their goal after 6 months, and cognitive improvement was found to be more important than either seizure or medication reduction in predicting the length of time a child remained on the diet.

Why would the ketogenic diet have such benefits? It is likely that this would be due, certainly in part, to seizures and/or medication dose being reduced, but this is difficult to asses, as children who do not show an improvement in seizure control do not usually continue on the diet for any significant length of time. Animal studies have attempted to answer this question, but show conflicting results. Whereas Murphy et al (2004) found ketogenic diet-treated rats to be more mobile than controls, thus less 'depressed', Zhao et al (2005) found their group of diet-treated rats to have significantly impaired visual-spatial learning and memory compared to rats fed a regular diet. Our study did not set out to examine the association between changes in alertness, awareness or responsiveness and seizure control, however results show that

these three functions were reported to be greatly improved in the majority of children, including many who did not have significant improvement in seizure control, as measured by greater than 50% reduction in baseline seizures. This was particularly noticeable at 3 months.

Other side effects in our study group were rare. During 12 month follow up, only one child presented with renal debris, thought to be at high risk of subsequent stone formation; this was less than 1% of our total sample. This is lower than other literature reports (Hertzberg et al, 1990; Furth et al, 2000; Kossoff et al, 2002; Sampath et al, 2007), however, the long-term risk was not assessed in our study. Hertzberg et al (1990) found the average time on the diet before kidney stone formation to be 17 ½ months; a longer follow up of our children may have increased the numbers seen with this side effect.

As a group, there were no significant abnormalities noted in the routine haematology or biochemistry. However, as found in many previous studies (Dekaban, 1966; Chesney et al. 1999; Vining 1999; Delgado et al, 1996, Kwiterovich et al, 2003; Keene et al, 2006), there were increases in plasma lipid levels during diet treatment. After 3, 6 and 12 months, cholesterol levels rose significantly in both diet groups, with 30-40% of children having a serum cholesterol level above the recommended higher limit. This pattern was different for triglycerides: levels rose significantly in the classical diet group, but not in the MCT group, and by 3 months of treatment, there was a highly significant difference in mean levels between the groups, which continued throughout the study duration. Over half of the classical group had a triglyceride level above the recommended higher limit at 3 months; this increased to over two thirds by 6 and 12 months. However, numbers with high levels in the MCT group fell during the study.

So what is the significance of these results? Our analysis would have been considerably improved if we had examined the lipoprotein fractions within the total cholesterol, as it is well known that raised very low density lipoprotein and low density lipoprotein cholesterol increase atherogenic risk, whereas raised high density lipoprotein has a protective influence. Kwiterovich et al (2003) did examine lipoproteins and apolipoproteins in ketogenic diet children, and found significant increases in the atherogenic lipoproteins and a decrease in the anti-atherogenic high density lipoprotein cholesterol. The question that is asked by not only scientific investigators, but also the parents and carers of many children is, does this increase the long-term risk of cardiovascular problems? It is known that in the general paediatric population, raised serum lipids and lipoproteins in childhood do tend to track into later life (Webber et al, 1991), but the relevance of this to our particular group with epilepsy is not known. An early case report suggested no evidence of adverse effects of the diet on cardiovascular function in adulthood (Livingstone, 1977), and a more recent study on long-term use of the diet suggests that lipid levels may trend back towards normal after two years (Groesbeck et al, 2006). As alterations in fatty acid intakes have been shown to influence plasma levels (Dahlin et al, 2007), it is certainly important that ketogenic diet children are given advice to maximise their intake of long-chain polyunsaturated fatty acids and reduce saturated fat sources wherever possible within the constraints of such a high fat diet, to try and reduce cardiovascular risk.

It is worth noting that a considerable number of our children had high levels of both cholesterol and triglycerides prior to starting dietary treatment. 11% of the classical diet group and 21% of the MCT diet group had a baseline cholesterol level above the recommended higher limit; just under a quarter of both groups had a

baseline triglyceride level above the recommended higher limit. Kwiterovich (2003) also found higher than average baseline triglyceride levels; this may be due to the ant-epileptic medications, and raises the question of pre-existing cardiovascular risk that these children may be exposed to prior to diet commencement. Indeed, in the MCT group, the proportion of children with triglyceride levels above recommended higher limits fell progressively from 24% to only 5% by 12 months on the diet.

The relevance of the differing effect of the two diet protocols on triglyceride levels is not easy to elucidate. There will be faster metabolic clearance of triglycerides provided by a MCT diet due to their faster digestion and absorption, but it is not clear how much the difference in levels between the two diets is due just to these metabolic differences, and how much they could actually benefit a child in terms of their cardiovascular risk. This certainly warrants further study, with a more detailed examination of the effect that the two diets have on not just total lipid levels, but their lipoprotein fractions as well.

This uncertainty aside, the tolerability results of this study have shown no differences between the classical and MCT diets that would indicate any clinical advantages in using one protocol above the other. This adds further weight to the conclusion that both diets have their role in the treatment of children with drug-resistant epilepsy.

APPENDIX – PARENT/CARER QUESTIONNAIRE

How are you doing on the ketogenic diet?

Name: **Date:**
Length of time on diet:

1. Has your child had any side effects on the diet, such as sickness, abdominal pain, diarrhoea, constipation or lack of energy? *(circle answer)*

1. NO ——→ *If answer is No, go to question 4*
2. YES
3.

(If answer is Yes, please complete questions 2 and 3)

2. What side effects have you noticed? *(circle answer)*

1. DIARRHOEA
2. VOMITING
3. ABDOMINAL PAIN
4. CONSTIPATION
5. LACK OF ENERGY
6. OTHER - *please specify*

3. Do you feel these problems are caused by the prescribed food, or the special drinks? *(circle answer)*

1. FOOD
2. DRINKS
3. BOTH

4. If your child has been more constipated on the diet - have they needed any medicines for this?

1. NO
2. YES - please specify which medicines.....

5. Would you say that your child was more hungry on the ketogenic diet than he/she was before it was started? *(circle answer)*

1. NO
2. YES

6. Is your child able to finish all the food and drink that he/she has been prescribed? *(circle answer)*

1. NO
2. YES

7. Is your child having problems with the taste of the special drinks prescribed on his/her ketogenic diet? *(circle answer)*

1. NO
2. YES

8. Is your child having problems with the taste of the food prescribed on his/her ketogenic diet? *(circle answer)*

1. NO
2. YES

9. Have mistakes been made with your child's diet, for example, eating extra foods? *(circle answer)*

1. NO
2. YES
3. DON'T KNOW

10. Are you having any problems understanding and using the exchange system and recipes given to you? *(circle answer)*

1. NO
2. YES

(If yes, please specify the nature of the problem)

11. Since starting the diet, have you noticed any changes in your child's level of alertness? *(circle answer)*

1. MORE ALERT
2. LESS ALERT
3. NO CHANGE

12. Since starting the diet, have you noticed any changes in your child's awareness of his/her surroundings? *(circle answer)*

1. MORE AWARE
2. LESS AWARE
3. NO CHANGE

13. Since starting the diet, have you noticed any changes in your child's level of responsiveness? *(circle answer)*

1. MORE RESPONSIVE
2. LESS RESPONSIVE
3. NO CHANGE

14. Are there any other changes that you have noticed in your child since starting the ketogenic diet? (eg. mood changes, tasks and activities he/she is doing differently). Please specify below:

18. Overall, how do you feel that being on the diet has affected your child's quality of life? *(circle answer)*

1. IT HAS IMPROVED
2. IT HAS WORSENED
3. NO CHANGE

19. Overall, how do you feel the ketogenic diet has affected your quality of life as a family? *(circle answer)*

1. IT HAS IMPROVED
2. IT HAS WORSENED
3. NO CHANGE

Thank you for your help

CHAPTER 5

GROWTH OF CHILDREN ON THE KETOGENIC DIET

Contents

5.1 Introduction

Feeding difficulties and poor growth are widespread amongst children with neurological problems. Studies on growth in epilepsy have provided conflicting results. Lower than average heights have been reported in children with epilepsy living in a residential school (Round, 1981; Robinson et al, 1983), but subsequent studies on children with epilepsy living at home did not find any deviations in linear growth patterns (Tada et al, 1986; MacArdle et al, 1987; Kurowski et al, 1993). At the outset of this study, the author conducted a cross-sectional growth survey of 124 children and young adults living in the residential centre from which we were additionally recruiting into our trial. Many individuals had poor linear growth; this was a particular problem in females and those between 14-17.9 years of age (Neal et al, 2003). It was concerning that, despite improvements in management of childhood epilepsy, the findings were similar to those reported 20 years ago. Multiple drug usage may cause particular problems; in one group of children who were found to have lower than normal height centiles, the individuals on a combination of two medications had greater deficits in height than children taking either of the drugs

separately (Guo et al, 2001). Other side effects of such medications can be weight changes. A problem in some children with epilepsy may be a tendency to obesity, which will be worsened by inactivity, poor diet and lack of exercise.

There have been concerns about the growth of children on the ketogenic diet. Many children trying this treatment will have severe epilepsy, with associated neurological problems that will increase risk of nutritional problems, even before a restricted diet is commenced. Five studies have reported growth data from children on the diet, all following the classical protocol; these are summarised in Table 5.1. Three of the five were retrospective reviews, and only one study (Vining et al, 2002) contained a reasonable number of children; after accounting for initial dropouts, all the others had less than 40 children in their sample. Although Couch et al, (1999) found children were able to maintain linear growth and weight percentiles after 6 months on the ketogenic diet, other results were less encouraging. Liu et al (2003) reported a decrease in weight, but not height centiles after 4 months. Three studies reported compromised linear growth (Vining et al, 2002; Williams et al, 2002; Peterson et al, 2005); this appeared to be more of a problem in the younger age group and after a longer time period on the diet. Growth data on MCT diet children is very limited, and there are no studies that examine the relation between calorie and protein intake and growth.

As part of the current study, the growth of children on both classical and MCT diets was investigated, using weight and height measures, and the association between growth and calorie and protein intake examined.

Table 5.1 Studies reporting growth of children on the ketogenic diet

Authors	No	Age	Diet	Study design	Measurements	Results
Couch et al, 1999	21	2-11-yrs	Classical	Retrospective review	Height & weight at baseline & 6 mo on diet (as centiles for age), calculation of weight-for-height percent standard (as a percentage of 50th centile value)	• Significant increase in weight and height over 6mo • No change mean weight and height centiles, no weight & height centiles lower than baseline at 6mo • No falling below 100% standard weight-for-height
Vining et al, 2002	237 (133 on diet at 1 yr, 76 at 2 yrs)	2mo-9.8 yrs	Classical	Prospective study of 4 age cohorts, excluded severe physical & cognitive impairments	Height & weight (as z-scores) at baseline, 3mo, 6mo, 1 yr, 2 yrs & 3 yrs on diet. Change in Z-score analysed by 4 age groups, also whether above or below median for age at baseline, also whether ambulant or communicating.	• Weight z-score - lower after 3 mo in all groups; stable after 3 mo if below median at baseline; decreased after 3 mo if above median at baseline (sig. difference). • Height z-score – no problems up to 6 mo, then declined. Sig. diff between groups above & below median at baseline. • No children lost more than 2 z-scores up to 2 yrs • More problems in younger age groups • Greater decline in weight z-scores if non-ambulant or non communicating.
Williams et al, 2002	21	1-15.5 yrs	Classical	Retrospective review	Height while on diet, for up to 2 yrs at unspecified intervals (as centiles for age)	• Height centile fell from baseline while on diet in 18 children (86%), by visit 1 in 15 (71%).
Liu et al, 2003	25	1-16 yrs	14 classical. 11 MCT	Prospective study	Weight & height at baseline and 4 mo on diet (as centiles for age),	• No change in height centiles after 4 mo on both diets • Weight centiles decreased by 10% on both diets after 4 mo, change more significant on classical diet
Peterson et al, 2005	57 (39 on diet at 6 mo, 33 at 12 mo)	11 mo-20 yrs	Classical	Retrospective review	Height & weight (as centiles for age & z-scores) at baseline, 6 mo & 12mo on diet. Weight-for-height centiles if under 2 yrs, BMI if over 2 yrs. Analysed by seizure control & ketosis level.	• Weight z-score – no significant change • Height z-score – significant.decrease from baseline – 12 mo, greatest fall between 6 mo & 12 mo • Weight-for-height centile - significant.decrease from baseline – 12 mo, BMI centile –no change • No relation between seizure control & growth • High ketosis group had lower weight & height z-scores at 6 & 12 mo than moderate ketosis group

5.2. Subjects and methods

All children enrolled into the ketogenic diet trial had weight and height measures performed at the initial screening visit, the diet initiation visit, and at each subsequent follow-up clinic visit. Hospital clinic nurses, under the supervision of the ketogenic diet study nurse, performed all growth measures. Although families were also encouraged to regularly weigh the children at home between clinic visits (weekly if possible) to monitor the appropriateness of the dietary prescription, only clinic growth data is used for this analysis. Weight was measured to the nearest 0.1kg, using digital scales that weighed the subject while seated. Children who were unable to sit unaided were weighed while held by a parent or carer; this person was then reweighed on the same scales without holding the child, and the difference between the two weights calculated to give the child's weight. The same set of scales was used for most of the children at the main hospital centre (Great Ormond Street); occasionally a different clinic area had to be used, however the weighing scales were all regularly cross calibrated according to hospital protocol. Children seen at the other two centres were weighed in the same way on similarly accurate sitting scales available at those sites, the same set of scales being used for all measures

Height was measured to the nearest 1mm in children who were able to stand using a wall-mounted stadiometer. Shoes were removed before the measurement. Children stood upright, looking straight ahead, with feet together and both heels and backs touching the upright back of the scale. Children who were unable to stand independently had their length measured. Three people were usually needed for this type of measurement (clinic nurse, ketogenic diet nurse and dietitian). The child was positioned on a flat surface with the head held lightly. The legs and back were held straight with toes pointing vertically, and length measured with a flexible tape

measure. This method could only be used if the child was able to lie flat; it was not possible to accurately monitor linear growth in a few children with severe scoliosis.

Weights and heights were compared with reference values by using standard deviation scores (Z-scores), which express the difference between the measurement of an individual and the median value of the reference population as a proportion of the standard deviation of the reference population. An excel add-on computer program, lmsgrowth, was used to convert the measures into Z-scores; (Cole TJ, Pan. H. lmsGrowth: an Excel add-in to convert measurements to Z-scores) this used British 1990 reference data (Freeman et al, 1995). Body mass index (BMI) (weight in kilograms divided by the square of height in metres) was calculated for all individuals. The expression of this index as a Z-score, using the same computer program, based on BMI reference curves for children and young adults (Cole et al, 1995), allowed the use of this index to assess body shape in terms of fatness/thinness.

In children that completed 12 months of the study, mean calorie and protein intakes per kilogram (kg) body weight were calculated, using the average of the values for calorie and protein that were prescribed for the child at each of four time points, diet initiation, 3 months, 6 months and 12 months. As detailed in chapter 2, a child would have an initial energy and protein prescription calculated at the outset of the study; this would then be adjusted as regularly as needed, depending on subsequent weight changes.

Statistical analysis: Statistical analyses were performed on the growth data as outlined below, in order to answer the following questions:

1. *What change, if any, occurred in the weight, height and BMI Z-scores of the children during ketogenic diet treatment?*

Student's paired t-tests were used to compare Z-scores for weight, height and BMI at diet initiation (Z-score0), and 3 months (Z-score3), 6 months (Z-score6) and 12 months (Z-score12). In children who continued the diet for 12 months, linear regression was used in each child separately to determine the gradient of the line of best fit of their serial weight Z-scores. The resulting gradient value was used to represent the overall change in weight in that child over the 12-month period. This process was also repeated for both height and BMI Z-scores.

2. *Did the sex, ambulatory status or age of the child influence growth?*

The unpaired t-test was used to compare mean Z-score0 values of girls and boys, and of the ambulant and non-ambulant groups (ambulant defined as being able to walk aided or unaided). Three age groups were defined, as for the initial randomization (2-6 years, 7-11 years, 12–16 years): analysis of variance was used to do the same baseline comparison between the three different age groups. The paired t-tests to examine differences in Z-scores for weight, height and BMI between initiation and 3, 6 and 12 months were performed separately for girls and boys, for whether the child was ambulant or non-ambulant, and for each of the three age groups. In the children who completed 12 months of treatment, the unpaired t-test was used to compare the mean gradient of the line of best fit of serial Z-scores for weight, height and BMI between girls and boys, and the ambulant and non-ambulant groups. Analysis of variance was used to do the same comparison between the three different age groups.

3. *Was there any correlation between baseline weight, height or BMI, and subsequent growth?*

The difference between Z-score values at initiation and 3, 6 and 12 months was computed for each child, for weight, height and BMI. Pearson correlation coefficient

was used to examine correlation between initiation (Z-score0) values and these differences. In the children who completed 12 months of treatment only, Pearson correlation coefficient was used to examine correlation between initiation (Z-score0) values and the gradient of the line of best fit of their serial Z-scores for weight, height and BMI. Two data groups were created for both weight and height values: children with initiation weight or height above median for age (Z-scores > 0), and children with initiation weight or height below median for age (Z-score < 0). The unpaired t-test was used to compare mean Z-score0 values between these two groups, and to compare the mean gradient of the line of best fit of serial Z-scores for weight, height and BMI between the two groups.

4. *Was there any difference between classical and MCT diet children?*

Mean Z-score0 values were compared between the two diet groups, using the unpaired t-test. The paired t-tests to examine differences in Z-scores for weight, height and BMI between initiation and 3, 6 and 12 months were performed separately for the two diet groups. In the children who completed 12 months of treatment, the unpaired t-test was used to compare the mean gradient of the line of best fit of serial Z-scores for weight, height and BMI between the two diet groups.

5. *Was there any association between growth and energy or protein intake?*

This was examined for the children who completed 12 months of treatment only. The mean energy and protein per kg intake over the 12 months was compared between the two diets, using the unpaired t-test. Pearson correlation coefficient was used to examine the correlation between the mean energy and protein intake per kg of a child, and the gradient of the line of best fit of their serial Z-scores for weight, height and BMI.

SPSS software version 13 was used for all statistical analysis.

5.2 ***Results***

A total of 75 children were included in the growth data analysis: 42 boys and 33 girls. 50 of these children were defined as ambulant, and 25 non-ambulant. 40 were aged between 2-6 years; 25 between 7-11 years, and 10 between 12-16 years. 37 were following the classical ketogenic diet, 38 the MCT. The full data on each child is given in the appendix to chapter 5. As not all children continued on the diet beyond 3 months, the number of children providing weight and height data at each time point fell as the study progressed. Accurate height/length measures were not possible in all children, and calculation of BMI was only possible where weight and height data were both present. Table 5.2 shows the number of children providing data at each time point, and summarizes Z-scores, with mean, standard deviation, maximum and minimum values.

Table 5.2. Children providing growth data at each time point, and summary Z-score values for weight, height and BMI

Time point	Measure	No. of children providing data	Minimum Z-score	Maximum Z-score	Mean Z-score	Std. Deviation
Initiation visit (Z-score0)	Weight	75	-4.100	3.283	.17224	1.478935
	Height	64	-3.690	2.890	-.10061	1.351129
	BMI	64	-3.370	3.001	.41112	1.346118
3-month visit (Z-score3)	Weight	74	-4.300	3.331	-.00885	1.340424
	Height	61	-3.850	3.690	-.16032	1.383647
	BMI	61	-3.150	2.561	.17218	1.223200
6-month visit (Z-score6)	Weight	59	-4.550	3.220	-.14419	1.372597
	Height	43	-4.060	2.820	-.27330	1.388418
	BMI	43	-3.210	2.452	.15760	1.251040
12 month visit (Z-score12)	Weight	40	-5.240	2.570	-.18950	1.532253
	Height	32	-3.880	2.300	-.50212	1.491335
	BMI	32	-4.640	2.150	.26182	1.349311

Changes in Z-score values for weight, height and BMI over the course of the study period were plotted for all children, to visualise any overall trends (figures 5.1 – 5.3).

Figure 5.1. Change in weight Z-score over time (n=75)

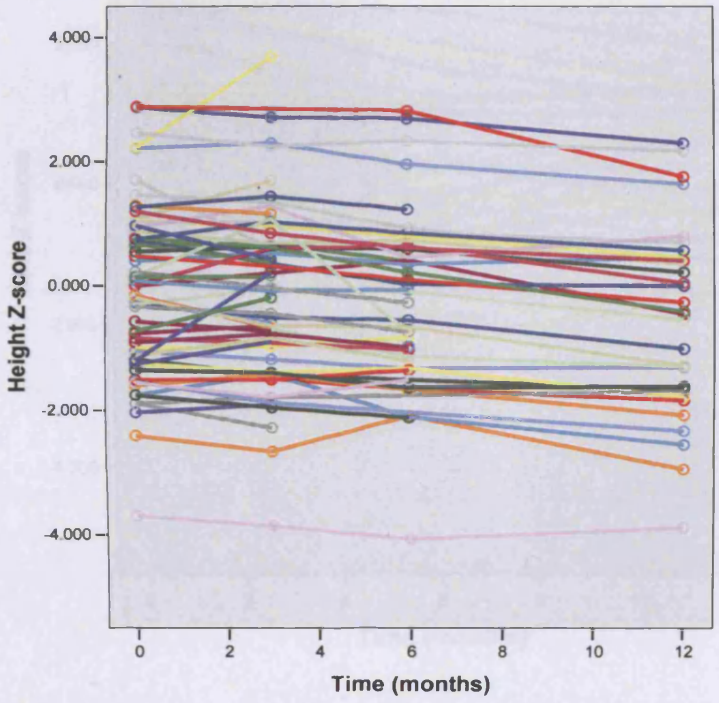


Figure 5.2. Change in height Z-score over time (n=64)

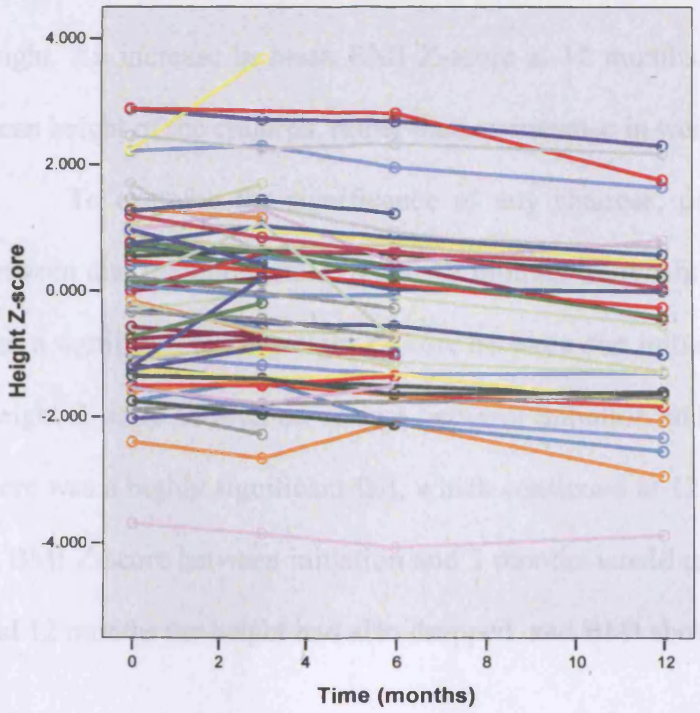
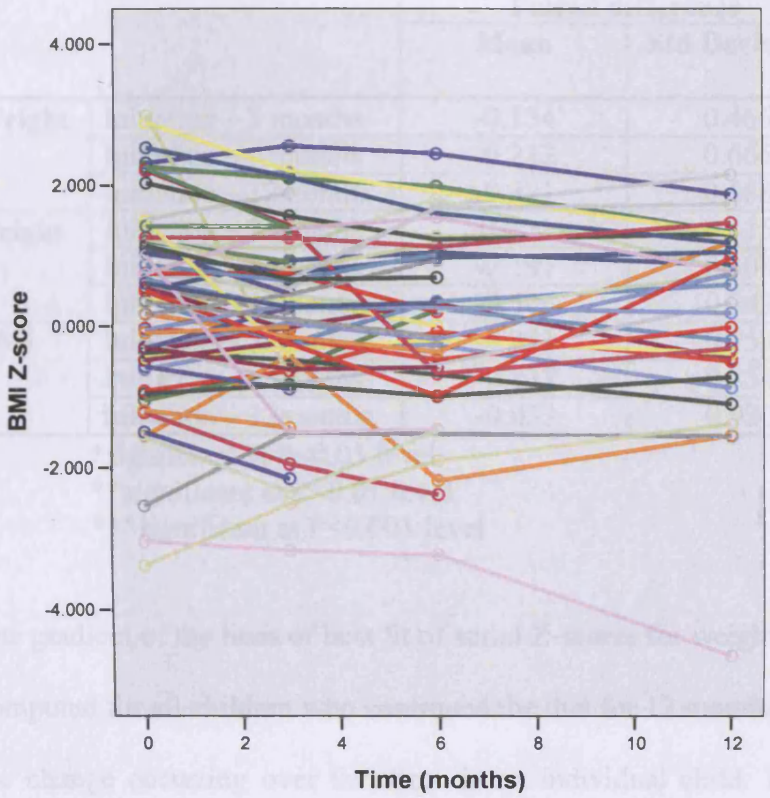


Figure 5.3. Change in BMI Z-score over time (n=64)



There is a general trend of falling weight and height Z-score during the course of ketogenic diet treatment. Changes in BMI Z-score are influenced by both weight and height. An increase in mean BMI Z-score at 12 months would be due to the fall in mean height of the children, rather than an increase in weight.

To examine the significance of any changes, paired differences in Z-score between diet initiation and 3, 6 and 12 months were computed (see Table 5.3). There was a significant fall in weight Z-score between diet initiation and 3, 6 and 12 months. Height Z-score showed no change between initiation and 3 months, but by 6 months there was a highly significant fall, which continued at 12 months. The significant fall in BMI Z-score between initiation and 3 months would reflect the fall in weight; by 6 and 12 months the height had also dropped, and BMI showed no significant change.

Table 5.3 Analysis of paired differences in weight, height and BMI Z-score.

		Paired difference		p value (2 tailed)
		Mean	Std Deviation	
Weight	Initiation – 3 months	-0.154	0.466	0.006**
	Initiation – 6 months	-0.213	0.665	0.017*
	Initiation – 12months	-0.321	0.588	0.001**
Height	Initiation – 3 months	0.004	0.415	0.947
	Initiation – 6 months	-0.187	0.303	0.000***
	Initiation – 12months	-0.506	0.343	0.000***
BMI	Initiation – 3 months	-0.221	0.753	0.027*
	Initiation – 6 months	-0.137	0.854	0.305
	Initiation – 12months	-0.033	0.920	0.838

*significant at P<0.05 level
**significant at P<0.01 level
***significant at P<0.001 level

The gradient of the lines of best fit of serial Z-scores for weight, height and BMI were computed for all children who continued the diet for 12 months, and used to represent the change occurring over that time in an individual child. The mean gradient for weight (n=40) was –0.0280 (range –0.17-0.06), for height (n=32) was –0.0434 (range –0.10-0.02), and for BMI (n=32) was –0.0044 (range –0.22-0.16), again indicating an overall downward trend in all growth Z-scores.

Influence of sex

Mean initiation weight, height and BMI Z-score values showed boys as a group to be slightly heavier, shorter and fatter than girls (see Table 5.4), but the differences were not significant (p=0.748, p=0.748, p=0.861 for weight, height and BMI Z-score respectively).

Table 5.4 Mean diet initiation Z-score values (Z-score0), subdivided by sex, ambulatory status, age group and diet.

Category	Mean Z-score0 value (no. providing data)		
	Weight	Height	BMI
Girls	0.110 (n=33)	-0.034 (n=26)	0.375 (n=26)
Boys	0.221 (n=42)	-0.146 (n=38)	0.436 (n=38)
Ambulant	0.357 (n=50)	-0.045 (n=48)	0.509 (n=48)
Non-ambulant	-0.198 (n=25)	-0.267 (n=16)	0.116 (n=16)
Age 2-6 years	0.616 (n=40)	0.264 (n=36)	0.666 (n=36)
Age 7-11 years	-0.281 (n=25)	-0.330 (n=19)	0.087 (n=19)
Age 12-16 years	-0.471 (n=10)	-1.072 (n=9)	0.078 (n=9)
Classical diet	-0.069 (n=37)	-0.391 (n=32)	0.330 (n=32)
MCT diet	0.407 (n=38)	0.190 (n=32)	0.492 (n=32)

Analysis of the paired differences in Z-scores between initiation and 3, 6 and 12 months separately for girls and boys showed the fall in weight Z-score between initiation and 3 months to be significant for boys (p=0.010) but not girls (p=0.206); this was also the case at 12 months (p=0.007 for boys and 0.068 for girls). Neither group had a significant change in height Z-score at 3 months. The fall in height Z-score between initiation and 6 months, although significant in both groups, appeared more marked in the boys (p=0.003) than the girls (p=0.037). This was also the case at 12 months (p=0.000 for boys and 0.002 for girls).

The mean gradients of the lines of best fit for serial Z-scores for weight, height and BMI were plotted for each sex separately in children completing the 12-month study period (see Table 5.5). There was no significant difference in mean gradient between girls and boys for weight (p=0.920), height (p= 0.732) or BMI (p= 0.923).

Table 5.5 Mean gradient of best-fit line values for weight, height and BMI Z-scores, in children completing 12 months of treatment.

Category	Mean gradient of line of best fit (number providing data)		
	Weight Z-score	Height Z-score	BMI Z-score
Girls	-0.0288 (n=18)	-0.0414 (n=14)	-0.0018 (n=14)
Boys	-0.0272 (n=22)	-0.0449 (n=18)	-0.0065 (n=18)
Ambulant	-0.0306 (n=29)	-0.0459 (n=24)	-0.0070 (n=24)
Non-ambulant	-0.0210 (n=11)	-0.0358 (n=8)	0.0033 (n=8)
Age 2-6 years	-0.0333 (n=23)	-0.0512 (n=21)	0.0027 (n=21)
Age 7-11 years	-0.0102 (n=12)	-0.0352 (n=7)	0.0029 (n=7)
Age 12-16 years	-0.0459 (n=5)	-0.0160 (n=4)	-0.0492 (n=4)
Classical diet	-0.0323 (n=19)	-0.0429 (n=17)	-0.0097 (n=17)
MCT diet	-0.0241 (n=21)	-0.0440 (n=15)	0.0015 (n=15)
Baseline weight Z-score<0	-0.0126 (n=18)	*	*
Baseline weight Z-score>0	-0.0405 (n=22)	*	*
Baseline height Z-score<0	*	-0.0404 (n=16)	*
Baseline height Z-score>0	*	-0.0464 (n=16)	*
Baseline BMI Z-score<0	*	*	0.0121 (n=13)
Baseline BMI Z-score>0	*	*	-0.0146 (n=19)
Total	-0.0280 (n=40)	-0.0434 (n=32)	-0.0044 (n=32)

Influence of ambulatory status

Ambulant children as a group were heavier, taller and fatter than their non-ambulant counterparts at baseline (see Table 5.4), but the differences in mean weight, height or BMI Z-score0 were not significant (p=0.126, p=0.574, p=0.316 respectively). Analysis of the paired differences in Z-scores between initiation and 3, 6 and 12 months separately for ambulant and non-ambulant groups showed the fall in weight Z-score between initiation and 3 months to be highly significant for the ambulatory group (p=0.000) but not the non-ambulatory group (p=0.334); this was also the case at

6 months (p=0.000 for ambulatory and 0.505 for non-ambulatory), and at 12 months (p=0.001 for ambulatory and 0.406 for non-ambulatory). A similar pattern of difference was seen with height Z-score: neither group had a significant change at 3 months, but by 6 months this fell significantly in the ambulatory group (p=0.000), but not in the non-ambulatory group (p=0.950). By 12 months, both groups had a significant drop in height Z-score, but this continued to be more marked in the ambulatory children (p=0.000 for ambulatory and 0.032 for non-ambulatory).

The mean gradients of the lines of best fit for serial Z-scores for weight, height and BMI were plotted for the ambulatory and non-ambulatory groups separately in children completing the 12-month study period (see Table 5.5). There was no significant difference in mean gradient between the two groups for weight (p=0.596), height (p= 0.386) or BMI (p= 0.777).

Influence of age

The children at diet initiation appeared as a group to get lighter, shorter and thinner with increasing age, with a progressive fall in mean Z-score for weight, height and BMI in the older groups (see Table 5.4). This difference was significant for both weight and height Z-score (p=0.018 for both), but not BMI Z-score (p=0.233). Analysis of the paired differences in Z-scores between initiation and 3, 6 and 12 months separately for the three age groups showed the fall in weight Z-score between initiation and 3 months to be significant in the 2-6 year old children (p=0.015) but not the older groups (p=0.593 for 7-11 year group, p=0.065 for 12-16 year group); this was also the case at 6 months (p=0.026 for 2-6 year group, p=0.506 for 7-11 year group and p=0.336 for 12-16 year group), and 12 months (p=0.006 for 2-6 year group, p=0.535 for 7-11 year group and p=0.074 for 12-16 year group). No age group had a

significant change in height Z-score at 3 months, but by 6 months this fell significantly in the 2-6 year group (p=0.016) and the 7-11 year group (p=0.024), but not in the 12-16 year group (p=0.099). Changes in height Z-score were similar at 12 months: this fell significantly in the 2-6 year group (p=0.000) and the 7-11 year group (p=0.025), but not in the 12-16 year group (p=0.126).

The mean gradients of the lines of best fit for serial Z-scores for weight, height and BMI were plotted for each age group separately in children completing the 12-month study period (see Table 5.5). There was no significant difference in mean gradient between the three age groups for either weight (p=0.305) or BMI (p=0.495), but this was significant for height (p= 0.044).

Influence of baseline weight, height and BMI

There was a highly significant negative correlation between weight Z-score at the initiation visit, and the subsequent difference between this value and the values for that child at 3 and 6 months; this correlation was still present at 12 months but not as significant (see Table 5.6). Therefore the higher the Z-score at baseline, the more likely a child was to have a lower, or more negative value for the change in Z-score, that is, to drop down the Z-scores with subsequent ketogenic diet treatment. This correlation was not present for height, however BMI showed a similar pattern as weight (see Table 5.6).

Table 5.6 Correlation between baseline Z-scores and subsequent change in Z-score between baseline and 3, 6 and 12 months

	Correlation between Z-score0 and change in Z-score between 0 and 3 months			Correlation between Z-score0 and change in Z-score between 0 and 6 months			Correlation between Z-score0 and change in Z-score between 0 and 12 months		
	Correlation coefficient	No.	p value	Correlation coefficient	No.	p value	Correlation coefficient	No.	p value
Weight	-0.425	74	0.000***	-0.464	59	0.000***	-0.329	40	0.038*
Height	-0.006	60	0.967	-0.155	42	0.328	-0.282	32	0.112
BMI	-0.444	60	0.000***	-0.357	42	0.020*	-0.467	32	0.006**

*significant at P<0.05 level
**significant at P<0.01 level
***significant at P<0.001 level

In children who completed 12 months of treatment, the correlation between weight Z-score at initiation visit, and the gradient of the line of best fit of serial weight Z-score values was not significant (see Table 5.7). This correlation was also non-significant for height, but just significant for BMI.

Table 5.7 Correlation between baseline Z-scores and gradient of line of best fit of serial Z-score values

	Correlation between Z-score0 and gradient of line of best fit of serial Z-score values		
	Correlation coefficient	No.	p value
Weight	-0.291	40	0.068
Height	-0.296	32	0.100
BMI	-0.411	32	0.020*

*significant at P<0.05 level

Children were divided into two groups, those with Z-scores above and below zero at baseline. At initiation 33 children had a weight Z-score less than zero and 42 had a Z-score greater than zero. The mean gradient of the line of best fit for serial Z-scores for weight was plotted for each group separately in children completing the 12-month

study period (see Table 5.5); there was no significant difference between the two groups (p=0.079). At initiation, 33 children had a height Z-score less than zero and 31 had a Z-score greater than zero. The mean gradient of the line of best fit for serial Z-scores for height was plotted for each group separately in children completing the 12-month study period (see Table 5.5); there was no significant difference between the two groups (p= 0.551). At initiation, 24 children had a BMI Z-score less than zero and 40 had a Z-score greater than zero. The mean gradient of the line of best fit for serial Z-scores for BMI was plotted for each group separately in children completing the 12-month study period (see Table 5.5); there was again no significant difference between the two groups (p= 0.358).

Differences between classical and MCT diet children

At diet initiation, the children randomized to start the MCT diet appeared as a group to be heavier, taller and fatter than the classical diet group (see Table 5.4), however differences in mean Z-score0 values were not significant for weight (p=0.165), height (p=0.085), or BMI (p=0.635). The changes in Z-score values over the course of the study period were plotted for the two diets separately (figures 5.4 – 5.6).

Figure 5.4. Change in weight Z-score over time in children on the MCT and classical ketogenic diets

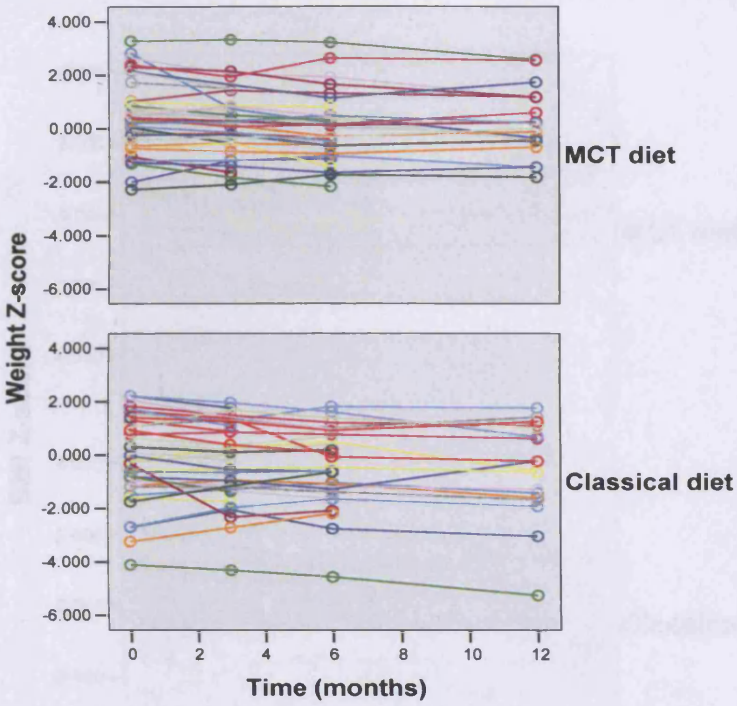


Figure 5.5. Change in height Z-score over time in children on the MCT and classical ketogenic diets

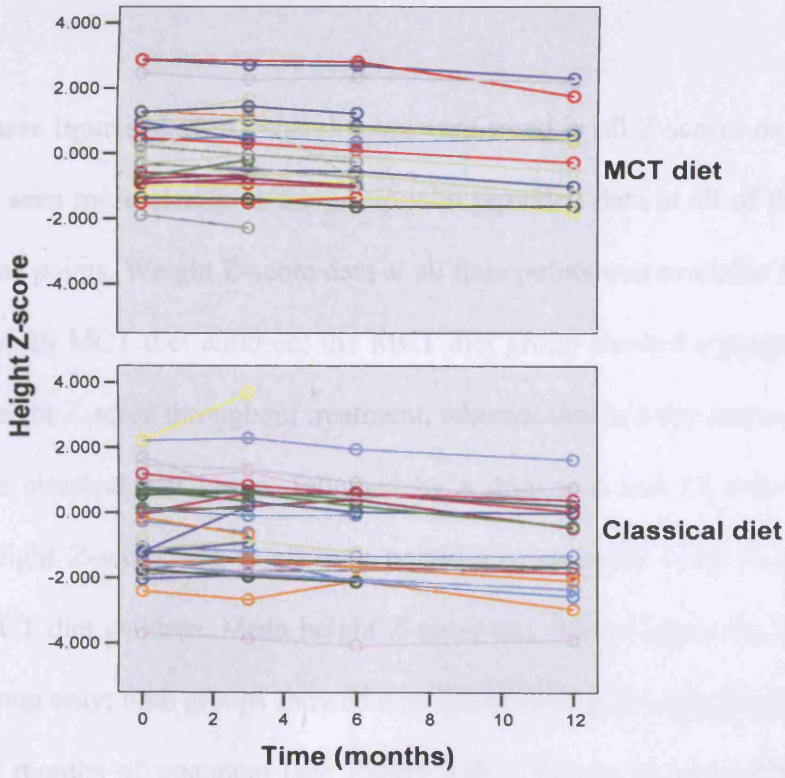
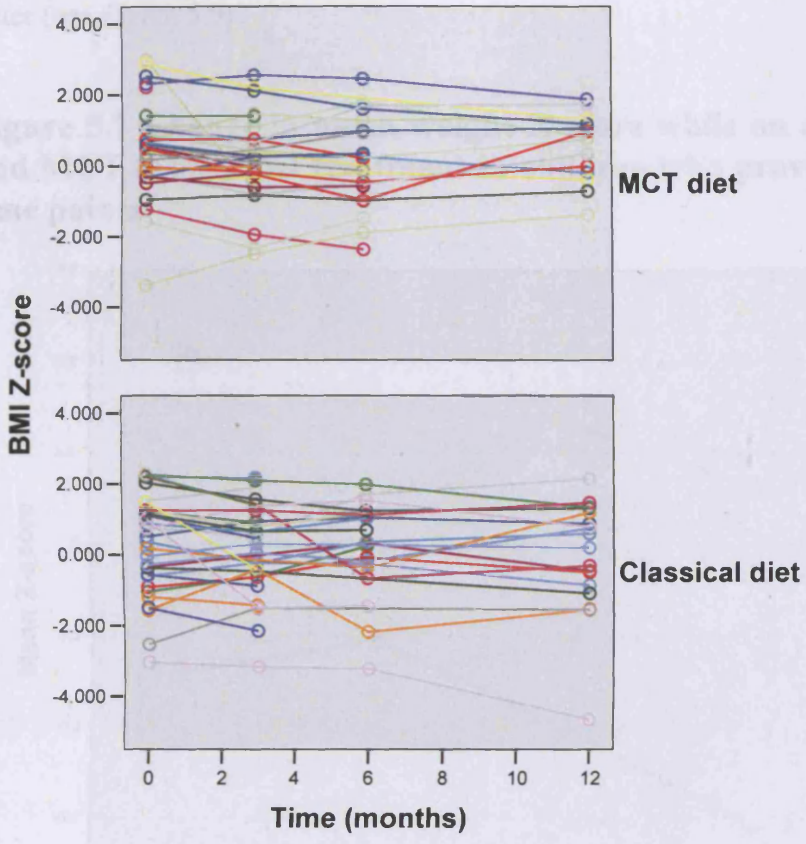


Figure 5.6. Change in BMI Z-score over time in children on the MCT and classical ketogenic diets



These figures show a general downward trend in all Z-scores on both diets. This can be seen more clearly in the group who provided data at all of the four measurement time points. Weight Z-score data at all time points was available from 19 classical diet and 20 MCT diet children; the MCT diet group showed a progressive drop in mean weight Z-score throughout treatment, whereas this initially increased after 3 months in the classical diet group, followed by a drop at 6 and 12 months (see Figure 5.7). Height Z-score data at all time points was available from 14 classical diet and 13 MCT diet children. Mean height Z-score had fallen slightly by 3 months in the MCT group only; both groups showed a progressive drop in mean height Z-score after 6 and 12 months of treatment (see Figure 5.8). Changes in mean BMI Z-score are again

difficult to interpret due to the influence of both weight and height; the classical group appeared to become thinner over the 12-month period, while the MCT group became fatter (see Figure 5.9).

Figure 5.7 Change in mean weight Z-score while on classical (n=19) and MCT (n=20) diet treatment in children who provided data at all time points

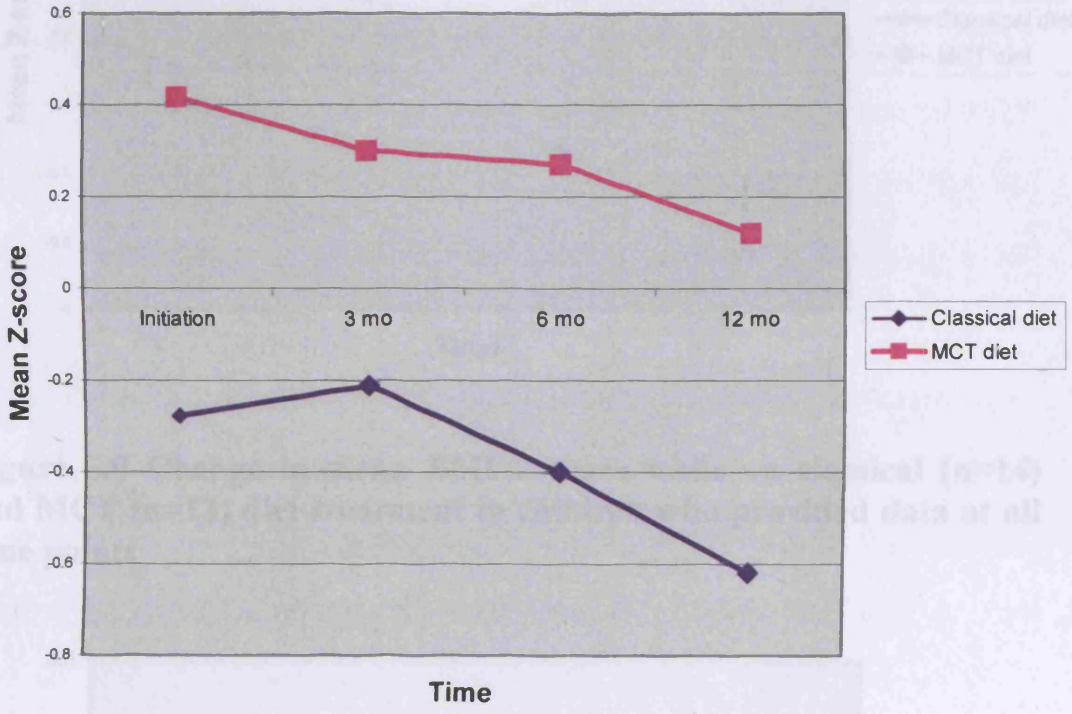


Figure 5.8 Change in mean height Z-score while on classical (n=14) and MCT (n=13) diet treatment in children who provided data at all time points

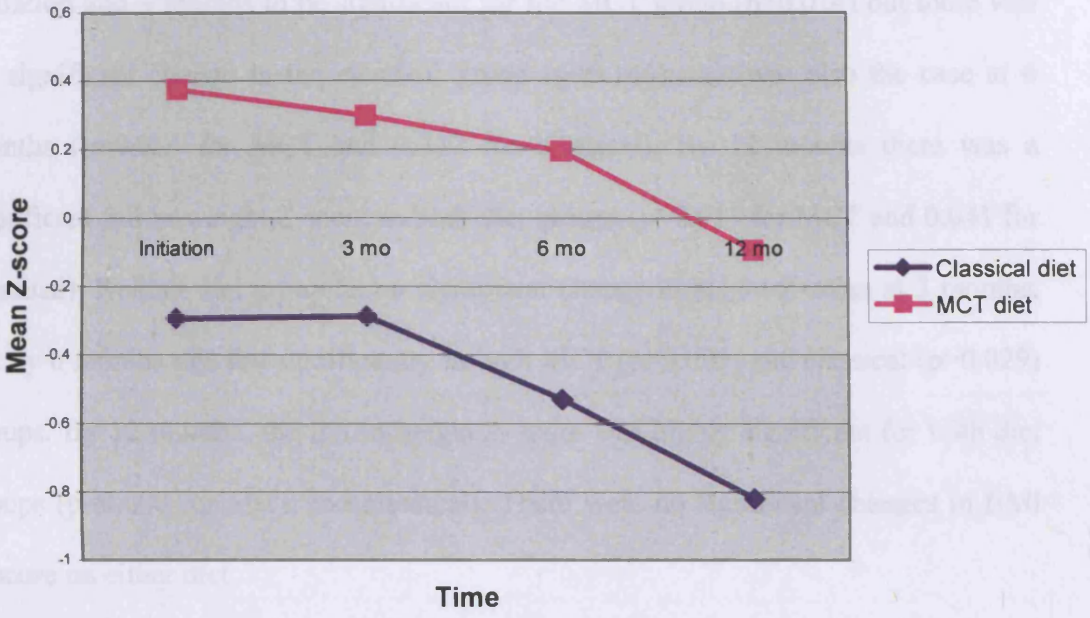
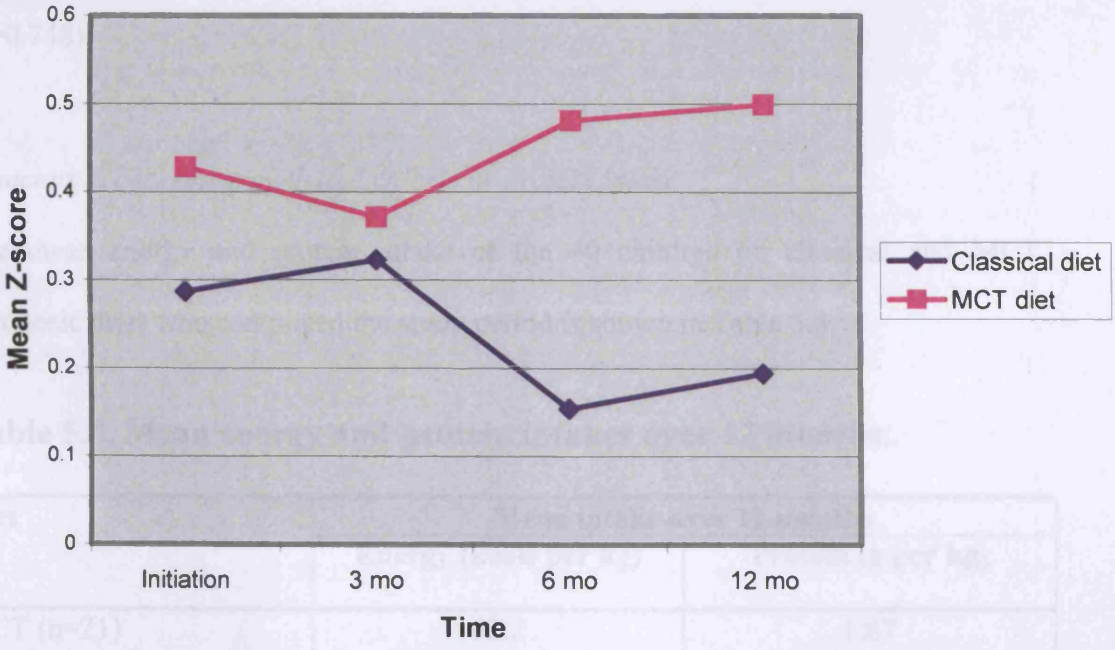


Figure 5.9 Change in mean BMI Z-score while on classical (n=14) and MCT (n=13) diet treatment in children who provided data at all time points



Analysis of the paired differences in Z-scores between initiation and 3, 6 and 12 months separately for the two diet groups showed the fall in weight Z-score between initiation and 3 months to be significant for the MCT group (p=0.014) but there was no significant change in the classical group (p=0.146); this was also the case at 6 months (p=0.014 for MCT and 0.332 for classical). By 12 months there was a significant fall in weight Z-score in both diet groups (p=0.014 for MCT and 0.041 for classical). Neither diet group had a significant change in height Z-score at 3 months, but by 6 months this fell significantly in both MCT (p=0.003) and classical (p=0.029) groups. By 12 months, the fall in height Z-score was highly significant for both diet groups (p=0.000 for MCT and classical). There were no significant changes in BMI Z-score on either diet.

The mean gradients of the lines of best fit for serial Z-scores for weight, height and BMI were plotted for each diet separately in children completing the 12-month study period (see Table 5.5). There was no significant difference in mean gradient between the two diet groups for weight (p=0.611), height (p=0.912) or BMI (p=0.748).

Association between growth and calorie or protein intake

The mean energy and protein intake of the 40 children on classical and MCT ketogenic diets who completed the study period is shown in Table 5.8.

Table 5.8. Mean energy and protein intakes over 12 months

Diet	Mean intake over 12 months	
	Energy (kcals per kg)	Protein (g per kg)
MCT (n=21)	63.2	1.67
Classical (n=19)	61.1	1.13
P value	0.651	0.000

There was no significant difference in mean energy intake over the 12 months between the two diets, but the MCT group had a significantly higher protein intake. There were no significant correlations between the mean energy or protein intake per kg of a child, and the gradients of the lines of best fit of their serial Z-scores for weight, height or BMI (see Table 5.9).

Table 5.9 Correlation between energy and protein intakes and gradient of line of best fit of serial Z-score values

	Correlation between mean energy intake (kcals /kg) and gradient of line of best fit of serial Z-score values			Correlation between mean protein intake (g/kg) and gradient of line of best fit of serial Z-score values		
	Correlation coefficient	No.	p value	Correlation coefficient	No.	p value
Weight	0.050	40	0.760	0.029	40	0.858
Height	0.448	32	0.108	-0.219	32	0.453
BMI	-0.206	32	0.479	-0.191	32	0.514

5.4. Discussion

The Z-score results for weight, height and BMI in these children on two ketogenic diets range widely, from below –3 to above 3; they are clearly a group of varying size and shape, who span the whole centile range. Although the use of mean Z-scores at each time point may be limited by differing numbers included at each point, they do indicate a downward trend in both weight and height during the course of the study. The paired differences show the fall in weight Z-score to be significant at all time points, and height highly significant by 6 and 12 months.

These results add further weight to the growing body of evidence that the ketogenic diet does appear to impact adversely on growth. Although some of the previous study results appear conflicting (see Table 5.1), a large part of the

discrepancy may be due to differing follow up measurement periods. Couch et al (1999) found no problems with either weight or height in their group of children after 6 months on the diet, and Liu et al (2003) found no height change after 4 months, but weight to decrease by 10%. These are short time frames within which to assess growth trends; any negative impact on longitudinal height gain will not usually be noticed until after a few months. In contrast, Williams et al (2002) reported height centiles to fall from baseline in 86% of their children after 24 months on the diet, and Peterson et al (2005) found height Z-score to show a significant decrease from baseline by 12 months, with the greatest fall between 6 and 12 months. No significant change was found in weight Z-score. Vining et al (2002), also reported height Z-score to show no problems up to 6 months, then to decline. It is clear that the more long-term the measurement period, the more accurately a conclusion can be reached about the impact of ketogenic diet treatment on growth.

Changes in BMI Z-score are more difficult to interpret; this is influenced by weight and height, changes in either resulting in a change in BMI. An overall fall in an individual's weight and height would be likely to manifest as no change in a BMI Z-score. Therefore there appeared to be no significant changes in BMI over the study period, similar results to Peterson et al (2005), who also reported using BMI centiles, and found no change after 12 months. The importance of BMI in dietary efficacy has been questioned: a recent study has shown no correlation between changes in BMI and seizure control in children on a ketogenic diet (Hamdy et al, 2007).

The use of a gradient of line of best fit of serial measures in children who completed 12 months of dietary treatment is recommended as the appropriate statistical methodology for this type of data (Matthews et al, 1990). This enables a mean gradient to be obtained for subgroups of children on the diet, which allows a

statistical comparison between these groups. Initially the fall in weight and height appeared more marked in boys, in the ambulant group, and in the younger children. When a mean gradient was obtained for each of these sub-groups, no significant differences were found between the sexes, or non-ambulant and ambulant groups. The three age groups had a significantly different height gradient, which fell with increasing age, indicating more of a fall in Z-score; this significance was not seen for weight. Vining et al (2002) also examined age and ambulatory status as variables. They reported similar problems in younger age groups, however found a greater decline in weight Z-scores if non-ambulant. This discrepancy in results may have been due to our ambulant group being heavier than their non-ambulant counterparts at baseline, thus having a lower calorie prescription at the outset.

It would certainly seem expected that changes in weight Z-score could be influenced by baseline weight. The correlation between weight and BMI Z-scores at initiation and subsequent changes in Z-score seen in our results would not be surprising; the heavier and fatter a child initially, the more likely a diet would be designed with less calories, so child would be expected to have poorer weight gain. When growth trends in our study were examined in the group completing 12 months, by gradients of the line of best fit of serial measures, there were no significant difference in mean gradients for any of the three Z-scores between groups above and below median at baseline for the respective growth indicator. This is in contrast to results reported by Vining et al (2002) who found that weight Z score remained stable after 3 months if weight was below median at baseline, but continued to decrease if weight was above median at baseline; this difference was significant. The differing results are likely to be due to our considerably smaller sample size. Vining et al (2002) had 133 children remaining on the diet at 12 months out of an initial 237. A

similar drop out rate occurred in our sample, with only 40 children providing weight data and 32 height data by 12 months. This is a clear limitation of our study, as sub-groups for statistical comparisons were small. It is likely that the difference in mean weight Z-score gradient would achieve significance with a larger sample. Indeed, the correlation between baseline weight Z-score and the gradient of the line of best fit of serial weight Z-score values was significant for BMI, and only just below significance for weight.

The use of a randomization process should equal out the two diet groups, so it was surprising to find the MCT group considerably heavier, taller and fatter than the classical group at initiation, even if this difference was not statistically significant. This difference may be responsible in part for the differing pattern of weight Z-score between children on the two diets. Weight Z-score appeared to initially increase in the classical diet group, the subsequent decline was not significant until 12 months on the diet; however it showed a significant fall at all time points in the MCT diet group. This was the opposite of results reported by Liu (2003) who found more problems with the classical diet group after 4 months. Early weight changes between the two diets would be expected, due to the differing nature of the initiation process. As detailed in chapter 2, MCT fat in our study is built up over a week or two, resulting in reduced calories, whereas the classical diet was commenced on a full energy prescription if tolerated. Details of dietary prescriptions used by Liu et al (2003) are not available: it may be they were more generous in calories on the MCT diet, with a quicker increase to full prescription. It has also been suggested that the differing metabolic pathways and energy costs of MCT metabolism may lead to enhanced thermogenesis, as compared to their long chain counterparts (Papamandjaris et al, 1998). If so, this would affect energy balance by increasing energy expenditure and

reducing weight gain in the MCT group A statistical comparison of weight Z-score between the two diet groups in children completing our study, using the mean gradients of line of best fit, showed no significant difference between the classical and MCT diet children. The pattern of change in height Z-score was very similar for the two diets, both showing significant decline by 6 and 12 months; again there was no significant difference between the mean gradients for height Z-score. There were no significant changes in BMI on either diet.

A limitation of our methodology was that the study did not collect data on pubertal staging. Although only 10 children were aged between 12-16 years old, a small number of this group may have gone through puberty, and this could be a potential confounder in the results that we have been unable to control for.

The mean energy intakes over 12 months in the group of 40 children who completed the study were not significantly different between the two diet groups, however, as would be expected from the differing nature of the dietary prescriptions, the MCT group had a significantly higher mean protein intake per kg body weight. Despite suggestions that a low protein intake may be a factor in poor growth on a ketogenic diet, the more generous protein allowance of the MCT diet in this study clearly did not improve outcome; growth was not significantly different between classical and MCT diet children. There also appeared to be no correlation between either the energy or protein intake of a child and the gradient of their lines of best fit for weight, height or BMI. This would throw into question the importance of a role that either of these two nutrients would have in determining the long-term growth outcome of a child on this diet, and raises the question of what else might be causing the problems. Could it be persistent high ketones, or some other, as yet unknown process having an influence? The question must also be asked – what would the

growth of this group be like had they not been on a ketogenic diet? The nature of epilepsy, frequent seizures, and anti-epileptic medications, all are known to adversely affect growth, and whereas the ketogenic diet clearly does play a part, without a much larger trial, designed to answer this question specifically, the extent will be unknown.

APPENDIX. Table A5. 1. Growth data for all children

Study No.	Diet	Sex	Ambulant	Z-score0			Z-score3			Z-score6			Z-score12			Age group*	Z-score0			Slope of best fit line for weight**	Slope of best fit line for height***	Slope of best fit line for BMI***	Mean kcals per kg**	Mean g protein per kg**
				Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI		Wt	Ht	BMI					
1	2	F	No	-1.995			-1.188			-1.138						2	<>0							
2	2	M	Yes	3.283	2.881	2.324	3.331	2.715	2.561	3.220	2.693	2.452	2.570	2.300	1.880	1	>0	>0	>0	-0.06	-0.05	-0.04	71.7	1.8
3	1	F	Yes	-0.260	0.650	-1.040	0.030	0.680	-0.610	0.430	0.400	0.240				1	<>0	>0	<0					
4	2	M	Yes	1.035	0.877	0.747	1.434	0.679	1.482	1.313	0.734	1.283	1.180	0.350	1.370	1	>0	>0	>0	0.00	-0.04	0.04	45.4	1.5
5	1	M	No	-0.195	-0.001	-0.345	0.279			0.520	0.413	0.331	-0.590	-0.450	-0.450	1	<>0	<0	<0	-0.04	-0.04	-0.01	76.0	1.2
6	2	F	Yes	-0.212	-0.998	0.383	-0.174	-0.968	0.409	-0.377	-0.828	0.020				2	<>0	<0	>0					
7	1	M	Yes	-1.487	-1.511	-0.906	-1.281	-1.483	-0.620	-1.024	-1.646	-0.067	-1.410	-1.830	-0.480	3	<>0	<0	<0	0.01	-0.03	0.04	46.2	1.0
10	2	F	Yes	0.676	0.399	0.673	0.371	0.528	0.277	0.030	0.350	0.260	-0.170	0.460	-0.190	3	>0	>0	>0	-0.07	0.00	-0.07	33.9	0.9
11	1	M	Yes	1.550	1.461	0.750	1.302	1.338	0.550	1.824	0.932	1.708	1.770	0.390	2.150	1	>0	>0	>0	0.03	-0.09	0.13	74.0	1.1
16	1	F	Yes	-1.133	-1.050	-0.603	-0.922	-1.176	-0.226	-1.060	-1.320	-0.260	-1.580	-1.300	-0.860	3	<>0	<0	<0	-0.04	-0.02	-0.03	41.7	0.9
17	1	M	No	-1.092	-1.177	-0.363	-1.344	-1.423	-0.468	-1.605			-1.920	-1.660	-1.090	1	<>0	<0	<0	-0.07	-0.04	-0.06	68.2	1.4
19	1	M	Yes	-2.694	-2.399	-1.548	-2.038	-2.653	-0.406	-2.750	-2.080	-2.160	-3.030	-2.940	-1.530	2	<>0	<0	<0	-0.05	-0.04	-0.04	80.1	1.4
20	2	F	No	0.411	0.036	0.610	0.190			0.350			-0.460			1	>0	>0	>0	-0.07			74.4	1.9
21	1	M	Yes	0.782	0.745	0.515	0.867	0.357	0.942	0.780	0.030	1.050	0.630	0.000	0.880	2	>0	>0	>0	-0.02	-0.06	0.02	60.5	1.0
22	2	F	No	1.732			1.500									2	>0							
23	2	M	Yes	0.374	-0.613	1.183	0.267	-0.690	1.108	0.490	-1.120	1.810	-0.360	-1.290	0.810	1	>0	<0	>0	-0.06	-0.06	-0.02	79.4	2.0
25	2	M	Yes	-1.310	-0.842	-1.212	-1.828	-0.914	-1.936	-2.180	-1.020	-2.360				2	<>0	<0	<0					
26	1	M	No	0.384			0.209									1	>0							
30	2	M	Yes	-1.047	-1.887	0.563	-1.640	-2.280	0.190							1	<>0	<0	>0					
31	1	M	Yes	-1.570	-2.030	-0.560	-1.710	-1.900	-0.880							3	<>0	<0	<0					
33	1	M	Yes	1.317	0.677	1.220	0.890	0.380	0.920							1	>0	>0	>0					
35	2	M	No	2.829	1.074	3.001	0.750	1.700	-0.680	0.200						1	>0	>0	>0					
36	2	M	Yes	-0.040	-0.760	0.560	-0.390	-0.640	-0.040							2	<>0	<0	>0					
37	2	F	Yes	-1.190	-1.240	-0.430	-1.200	-1.380	-0.310	-1.030	-1.310	-0.180	-1.450	-1.770	-0.370	1	<>0	<0	<0	-0.02	-0.04	0.00	76.4	1.9
38	2	F	Yes	0.050			-0.550									3	>0							

Study No.	Diet	Sex	Ambulant	Z-score0			Z-score3			Z-score6			Z-score12			Age group*	Z-score0			Slope of best fit line for weight**	Slope of best fit line for height***	Slope of best fit line for BMI***	Mean kcals per kg**	Mean g protein per kg**
				Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI		Wt	Ht	BMI					
39	2	F	Yes	0.310	0.480	-0.020	0.120	0.320	-0.160	-0.300	0.100	-0.460	-0.120	-0.260	0.000	2	>0	>0	<0	-0.04	-0.06	0.00	67.2	1.7
40	1	M	Yes	-0.940	-1.750	0.370	-1.120	-1.410	-0.240	-1.160	-2.100	0.360	-1.260	-2.550	0.600	1	<>0	<0	>0	-0.02	-0.08	0.04	75.6	1.2
43	1	M	Yes	2.220	1.700	1.520	1.770	0.590	1.890							1	>0	>0	>0					
45	1	F	No	1.540	-0.260	2.210	1.260	-0.600	2.180							1	>0	<0	>0					
48	1	F	Yes	1.840	0.550	2.040	1.500	0.630	1.570	1.230	0.590	1.240	1.090	0.220	1.320	1	>0	>0	>0	-0.06	-0.03	-0.06	52.2	1.1
49	2	F	No	-0.110			-0.390									2	<>0							
50	1	F	No	-0.810	-1.590	0.190	-0.950	-1.420	-0.140	-1.270	-1.650	-0.350	-0.210	-2.070	1.210	1	<>0	<0	>0	0.05	-0.05	0.09	71.0	1.1
51	1	M	Yes	-4.100	-3.690	-3.020	-4.300	-3.850	-3.150	-4.550	-4.060	-3.210	-5.240	-3.880	-4.640	3	<>0	<0	<0	-0.10	-0.02	-0.14	83.2	1.5
52	2	M	Yes	0.580	-0.290	1.040	0.240	-0.510	0.760	0.390	-0.550	0.980	0.200	-1.010	1.060	1	>0	<0	>0	-0.02	-0.06	0.01	79.0	1.9
53	2	F	Yes	0.410	-0.300	0.900	0.280	-0.040	0.450	0.110	-0.090	0.230	0.240	-0.540	0.750	1	>0	<0	>0	-0.01	-0.03	-0.01	60.6	1.7
55	1	M	No	-0.570			-0.490			-0.440			-0.620			2	<>0			-0.01			47.1	1.0
57	1	F	No	1.660	0.010	2.220	1.390	0.600	1.440	-0.050	0.640	-0.660	-0.210	0.050	-0.300	1	>0	>0	>0	-0.17	-0.01	-0.22	50.5	1.1
59	1	F	No	-2.680	-1.890	-2.530	-1.960	-1.790	-1.500	-1.640			-1.910	-1.690	-1.550	2	<>0	<0	<0	0.06	0.02	0.06	53.2	1.0
60	1	M	Yes	0.090	-1.250	1.120	-0.190	-0.900	0.470							2	>0	<0	>0					
61	1	F	Yes	2.220	0.770	2.270	1.970	0.620	2.100	1.620	0.220	1.990	0.690	-0.410	1.350	1	>0	>0	>0	-0.13	-0.10	-0.08	55.8	1.0
62	1	M	Yes	0.310	-1.120	1.250	0.110	-0.840	0.800	0.190	-1.190	1.180				3	>0	<0	>0					
64	2	M	Yes	-0.630	-0.570	-0.470	-0.550	-0.730	-0.210	-0.630			-0.430			2	<>0	<0	<0	0.01			58.6	1.4
66	2	M	Yes	2.660	1.040	2.900	2.050	0.970	2.210	1.930			1.170	0.460	1.330	2	>0	>0	>0	-0.12	-0.05	-0.12	49.1	1.2
67	2	F	Yes	-0.230	-1.500	0.760	-0.220	-1.500	0.760	-0.660	-1.340	0.220	-0.470			3	<>0	<0	>0	-0.02			31.6	0.9
71	1	M	Yes	0.650	0.080	0.880	0.390	-0.080	0.650	0.700	-0.060	1.030				3	>0	>0	>0					
73	2	M	Yes	0.420	1.020	-0.210	0.070	1.020	-0.810	0.140	0.850	-0.530	0.590	0.700	0.340	2	>0	>0	<0	0.02	-0.03	0.06	59.9	1.5
75	1	F	Yes	1.090	2.220	-0.280	1.330	2.300	0.050	1.020	1.960	-0.170	1.420	1.640	0.750	1	>0	>0	<0	0.02	-0.05	0.08	65.0	1.2
76	2	M	Yes	-1.260	-1.350	-0.950	-1.400	-1.390	-0.820	-1.660	-1.630	-0.980	-1.450	-1.610	-0.710	2	<>0	<0	<0	-0.02	-0.02	0.02	65.5	1.7
79	1	M	No	-0.810	-0.150	-1.180	-1.350	-0.670	-1.420							1	<>0	<0	<0					
80	1	F	No	1.050	0.950	0.750	1.700	1.290	1.390	1.390	0.460	1.550	1.040	0.810	0.790	1	>0	>0	>0	-0.02	-0.03	-0.01	54.0	1.0
82	2	M	Yes	2.320	0.750	2.540	2.150	1.030	2.120	1.650	0.850	1.610	1.170	0.570	1.190	1	>0	>0	>0	-0.10	-0.02	-0.11	71.2	2.0
83	2	M	Yes	-0.790	0.160	-1.560	-0.530	1.080	-2.330	-1.430	-0.740	-1.470				1	<>0	>0	<0					

Study No.	Diet	Sex	Ambulant	Z-score0			Z-score3			Z-score6			Z-score12			Age group*	Z-score0			Slope of best fit line for weight**	Slope of best fit line for height***	Slope of best fit line for BMI***	Mean kcals per kg**	Mean g protein per kg**
				Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI	Wt	Ht	BMI		Wt	Ht	BMI					
84	1	M	Yes	1.420	1.200	1.270	1.270	0.850	1.260	0.940	0.610	1.140	1.260	0.410	1.480	2	>0	>0	>0	-0.01	-0.06	0.02	53.5	1.1
85	2	F	Yes	0.220	0.220	0.170	0.250	-0.040	0.450	0.480	-0.270	0.940	0.200			1	>0	>0	>0	0.00			62.9	1.7
86	2	M	No	0.510	0.970	-0.310	0.510	0.430	0.280							1	>0	>0	<0					
88	1	M	Yes	1.730	0.140	2.240	1.100	0.150	1.410							1	>0	>0	>0					
89	2	F	No	-2.280	-0.190	-3.370	-2.100	-0.640	-2.490	-1.740	-0.660	-1.890	-1.830	-1.270	-1.370	1	<>0	<0	<0	0.04	-0.08	0.16	93.5	2.5
91	2	F	Yes	-0.730	-0.910	-0.290	-0.860	-0.770	-0.600	-0.950	-0.980	-0.570	-0.700			2	<>0	<0	<0	0.00			69.8	1.7
92	1	F	No	2.080	2.230	1.500	1.440	3.690	-0.410	0.990						2	>0	>0	>0					
93	2	F	Yes	2.150	2.890	0.510				1.140	2.820	-0.970	1.730	1.760	0.980	1	>0	>0	>0	-0.04	-0.09	0.04	68.2	2.1
94	2	M	No	-0.410			-0.330			-0.330	-0.970	0.300	0.010			2	<>0			0.03			38.7	1.1
95	2	M	Yes	2.400	2.460	1.150	1.940	2.250	0.670	2.630	2.330	1.680	2.540	2.170	1.740	1	>0	>0	>0	0.03	-0.02	0.07	69.7	1.8
97	1	M	No	-1.180	-1.530	-0.040	-1.210	-1.870	0.310	-1.380			-1.660	-2.330	0.200	1	<>0	<0	<0	-0.04	-0.06	0.01	53.1	1.1
98	1	F	Yes	-0.020	-1.750	1.150	-0.540	-1.950	0.670	-0.610	-2.110	0.700				2	<>0	<0	>0					
99	2	F	No	0.860			0.510			0.300						1	>0							
100	2	M	Yes	0.750	1.300	-0.080	0.700	1.160	0.000							1	>0	>0	<0					
101	1	F	No	-0.310	-1.550	1.010	-2.310	-1.780	-1.490	-2.070	-1.500	-1.440				1	<>0	<0	>0					
103	2	F	Yes	1.020	1.270	0.620	0.860	1.440	0.280	0.820	1.230	0.340				2	>0	>0	>0					
104	1	M	Yes	0.940			0.400	0.140	0.450	0.100						1	>0							
108	1	F	No	-0.610			-0.650			-0.590						1	<>0							
110	2	M	Yes	2.130	0.770	2.230	1.480									3	>0	>0	>0					
111	2	F	Yes	0.090	-0.340	0.350	-0.140	-0.450	0.110	-0.470	-0.740	-0.140				2	>0	<0	>0					
112	1	M	No	-1.740	-1.200	-1.490	-1.150	0.210	-2.140	-0.630						2	<>0	<0	<0					
118	1	F	No	-3.220			-2.700			-2.160						2	<>0							
119	2	M	Yes	0.480	-0.730	1.430	0.840	-0.190	1.420	0.450						1	>0	<0	>0					

* 1 = 2-6yrs, 2 = 7-11 yrs, 3 = 12-16 yrs

** Only included if provided 12 month data for weight Z-score

*** Only included if provided 12 month data for height Z-score

CHAPTER 6

CONCLUSION AND THE WAY FORWARD

Contents

6.1. What have we achieved?

This study is an exciting contribution to the ketogenic diet literature. It is the first randomized controlled trial that has been conducted on this treatment, and is therefore the strongest scientific study to date and an extremely important milestone in the history of the diet. It is clear evidence that the diet does work, and should be routinely included in the treatments available for all children with intractable epilepsy. Although the classical diet may induce greater ketosis in children, there does not appear to be any significant advantage of using either the classical or MCT diet protocols in terms of either efficacy or tolerability. The impact of the diet on growth trajectories over the 12 months is also not significantly different between the two protocols. It is clear from these results that both ways of doing the diet have their place in the treatment of this group of children.

The achievements of the study are not limited to these results alone. Over the past six years, there has been a considerable change in awareness of the ketogenic diet in the UK. Publicity about the trial, both among health professionals and the media, has increased knowledge of the treatment. The development of a ketogenic diet charity by a mother of one of our study children has also made a significant contribution to the demand for this treatment. The charity, set up to provide support,

information, and dietary accessibility for families throughout the UK, has seen a huge growth over the past two years, and has been able to provide funding for some individual children to do the ketogenic diet, grants to enable more dietetic hours in certain hospitals, and for further research. The electronic ketogenic diet calculator (EKM) that was developed by the author in conjunction with a computer programmer has also contributed to these changes taking place. By allowing dietitians to calculate recipes at a fraction of the speed of hand calculations, and by also empowering many families with the freedom to calculate their own meals, this has released considerable dietetic time, enabling more children to be given the chance to try the diet. In addition, the Ketogenic Diet Professional Advisory Group (ketoPAG) of the UK has seen expansion of both numbers and activities, the latter including organisation of two national and a recent international conference. These far-reaching effects of our study have been very encouraging

6.2. Where do we go from here?

So what is the way forward? This will be in two main areas – research and education. There are a number of areas where future research would be very beneficial. The current study has only assessed children up to 12 months on treatment. After this, they were transferred to their local centres for on-going follow-up. It was not possible to continue diet monitoring of all children at the main study centre due to lack of NHS resources; this transfer was agreed with local centres prior to any child starting a ketogenic diet. As the most important outcome when measuring efficacy will be prolonged periods of seizure remission (Chadwick, 1997), an obvious follow-on to this study would be the research review of children at 24 months post diet initiation, and at further time points beyond then if possible. Other studies have shown

continued favourable outcome after 12 months, both in children who continued the diet for 12 months (Hemingway et al, 2001), and those who discontinued it earlier (Marsh et al, 2006). Although similar success rates in our children were hoped for, there is concern that many children have not done so well if transferred to a local centre with limited ketogenic diet experience. Some have actually discontinued successful diet treatment due to a lack of support from their local team. The extent of any problems in this area do need to be examined, to ensure no unnecessary loss of the benefits that many children have obtained from their first year on the diet. However it is not possible from our study to recommend an ideal length of time that a child should continue on the diet. Whereas some children who have become seizure free will be able to discontinue treatment after a couple of years without any recurrence of problems, many other children will need to stay on the diet for much longer to sustain the benefits. Further research into this area will help answer these questions.

Our study only included children over 2 years of age. It has already been speculated that the exclusion of younger children may have gone some way to explain differences in our results from some other published studies. The diet has been shown to be extremely successful in infants (Nordli et al 2001, Kossoff et al 2006), and it would be important to include this group in future randomized controlled trials.

Since commencing this study, there have been reports of different types of 'ketogenic style' diets, without such strict dietary regimens, that may also be of benefit for seizure control in children with intractable epilepsy. A modified Atkins diet, very low in carbohydrate, but without calorie, protein or fluid restriction has been shown to be effective (Kossoff et al, 2006; Kang et al, 2007). A low-glycaemic index treatment, with more liberal total carbohydrate but restricted to the low

glycaemic index varieties, has also been successful in 20 patients (Pfeifer & Thiele, 2006). It is likely that different types of diet will suit different types of patient, depending on age, food preferences, feeding method and family circumstances. Future research on these other types of dietary treatments for epilepsy, as compared to the two more established classical and MCT ketogenic diets, will enable more patient choice and tailoring to individual needs.

The education of relevant health professionals, mainly dietitians and paediatricians or paediatric neurologists, is essential to increase both acceptability and availability of the ketogenic diet, and thus meet the demand for this treatment. The education of dietitians is of particular concern to the author. There is very scarce literature that provides a practical guide to how to implement the ketogenic diet in practice. This is limited to a chapter in the dietitian's paediatric handbook (Neal & MacGrath, 2007), and an American handbook (Freeman, Freeman & Kelly, 2000), the latter based only on the classical diet and using American food values. The lack of information on the MCT diet is especially worrying. Identifying the importance of a stricter approach to management of this protocol, alongside a more flexible approach to its fine-tuning, especially with adjustments to the proportion of energy provided from the MCT fat, has already been discussed. The author strongly believes that this will contribute to maximizing both efficacy and tolerability of this version of the ketogenic diet.

The concern about the lack of support that some ketogenic diet children have received when transferred to their local hospital has been highlighted. There are also many children across the UK who have been unable to try the treatment, or who have seen long delays in initiating it, due to the lack of resources and education of local teams. It is hoped that the development of national educational resources related to the

implementation of both types of ketogenic diet in the UK will be a follow on from this work. There is a need to develop best practice protocols for diet calculation, initiation, maintenance, and monitoring. Questions to be addressed include who should do the diet, and where? Should this treatment be available only in specialist centres, or more widely across the country? The vision is that this educational work will be done in conjunction with both the parents charity and ketoPAG, and will include the regional training of dietitians and other health professionals where needed. This study has been just the beginning of what is an exciting time in the history of the ketogenic diet in the UK, and has provided a stepping-stone from which it can now continue to move forward in many directions.

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